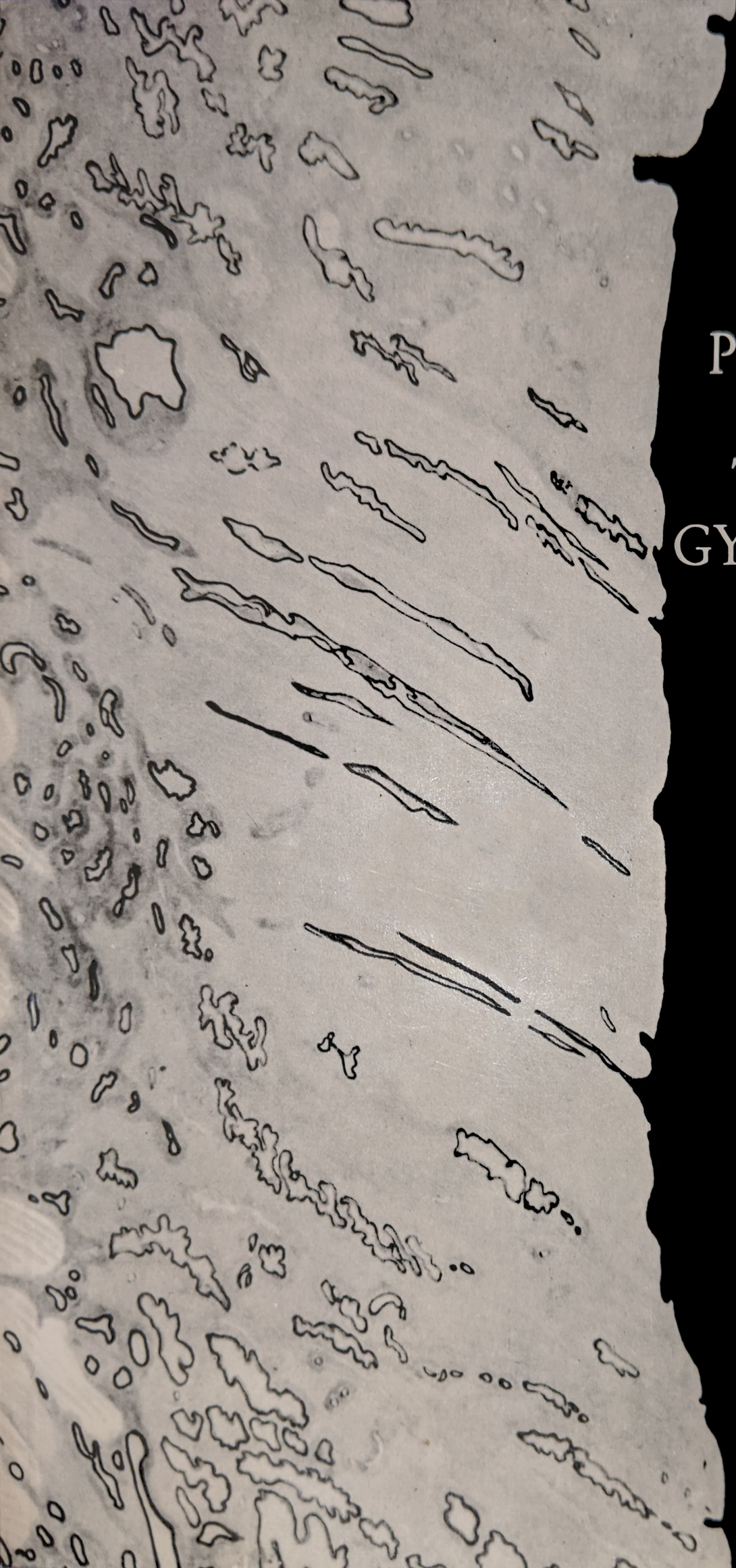

JOACHIM UFER

# THE PRINCIPLES AND PRACTICE OF HORMONE THERAPY IN GYNECOLOGY AND OBSTETRICS

WALTER DE GRUYTER & CO
BERLIN 30

Joachim Ufer

Hormone Therapy in Gynaecology and Obstetrics

In an endeavour to provide the doctor with information on the advances in endocrinological research and practice, we have made available for free distribution part of this edition of
"Hormone Therapy in Gynaecology and Obstetrics".

In this way we hope to make a contribution to modern gynaecological hormone therapy.

SCHERING AG Berlin

The Principles and Practice of

# Hormone Therapy in Gynaecology and Obstetrics

by

Dr. Joachim Ufer

82 Figures

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# Preface

## Preface of the English Edition

"Hormone Therapy in Gynaecology and Obstetrics" now appears for the first time in the English language, 10 years after the publication of the first German edition. This first English edition corresponds to the third German and the second Spanish editions.

The translation of specialized German language medical books into English occurs relatively infrequently, since there is a wide range of instructive and reference books in all medical specialities already available in English. We are under the impression that international contact as well as the exchange of experience and opinions between English and German speaking scientists in the last decade has considerably increased and gained in importance.

This development has encouraged the publisher and the author, to prepare an English language edition.

For the translation of this book we are greatly indebted to Dr. Frank Loeffler.

Berlin, autumn 1968 Joachim Ufer

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# A. Classification of Hormones

## I. Introduction

The concept of internal secretions was introduced by *Claude Bernard*. He described it as the process whereby certain cells control vital processes and physiological activity at remote sites by excreting organic substances into tissue fluid.
*Bayliss* and *Starling* later called these substances *hormones*.
We recognise not only hormones which are produced by endocrine glands (and enter the circulation without passing through a duct), but also secretions from exocrine glands which do have ducts. The latter will not be considered in this book although the substances they produce resemble hormones in that they both, in relatively small amounts, can influence many physiological processes by a catalyst-like action.

## II. Steroid Hormones

Steroid hormones are derived from '*Sterane*' and are soluble in fat. They are formed by the gonads, the adrenals and the placenta.

Table 1. *Site of Steroid Hormone Formation*

| Ovary | Testes | Adrenals | |
|---|---|---|---|
| + + | + | + | Oestrogens |
| + | + + | + + | Androgens |
| + + | — | + | Progestogens |
| — | — | + + | Glucocorticoids |
| — | — | + + | Mineralocorticoids |

They can be divided into the following groups: oestrogens, progestogens, androgens, glucocorticoids and mineralocorticoids. It should be noted that some steroids belong to more than one group.

**Example:** Desoxycorticosterone is a mineralocorticoid whose acetate derivative has a significant progestational action.

In addition, some steroids diminish or cancel out the effect of steroids from another group, and this phenomenon depends on the dose relationship between competing substances.

**Example:** At higher dosage levels, progestogens and androgens have an anti-oestrogenic effect.

The last decade has seen so marked an increase in the number of steroids recognised that the following subclassification is appropriate:

1. *Naturally occurring steroid hormones* formed in the adrenals, gonads and the placenta.

2. *Their intermediary metabolites* which are found in the blood, the liver or in urine.

3. *Steroids obtained by chemical reactions* (e.g. esterification or attachment of a methyl group, an ethyl group, or a halogen atom to one or more carbon atoms). Although their action and structure are related to the parent substances in groups 1 and 2, these products do not occur naturally. Their therapeutic use is, therefore, not strictly speaking, "hormone therapy".

## III. Protein Hormones

Unlike steroids, these substances, which are of protein character, are soluble in water. Their synthesis and purification, made difficult by their large molecular weight have, to date, only been achieved with hormones from the posterior pituitary, with adrenocorticotrophic hormone (ACTH), and insulin.

### a) Hypophyseal Hormones

A probable total of 10 different hormones is found in the three parts of the hypophysis cerebri (pituitary). Hormones numbered 1, 2, 4, and 5 in Table 2 are "trophic", i.e. they control the function of other endocrine glands. By contrast, growth hormone, as well as the hormones produced by the pars intermedia and the posterior pituitary exert their action on tissues directly. The primary action of prolactin (or luteotrophic hormone, LTH) is on the lactating breast. It is not known whether LTH has any trophic effect on the corpus luteum of the non-pregnant woman.

In addition to the above hormones, a number of other "trophic" substances have been described e.g. diabetogenic, anti-insulin, erythropoietic, fat-mobilising and exophthalmic hormones. The relevant publications, some of which deal more with hypothesis than fact, have not led to universal recognition of these substances. FSH and ICSH, both of which are important in gynaecology, derived their names from their effects on gonadal function. The restricted amounts of FSH that can be extracted from human pituitaries or menopausal urine (HMG) limits the therapeutic use of these hormones.

Table 2. *Pituitary hormones*

| Anterior lobe | Middle lobe | Posterior lobe |
|---|---|---|
| A. Gonadotrophic hormones | Melanophore stimul. hormone (Intermidine) | 1. Antidiuretic hormone |
| 1. Follicle stim. hormone (FSH) | | 2. Oxytocin |
| 2. Luteinising hormone (LH) = interstitial cell stim. hormone (ICSH) | | 3. Vasopressin |
| 3. Luteotrophic hormone (LTH) = Prolactin | | |
| B. Hormones affecting metabolism | | |
| 4. Adrenocorticotrophic hormone (ACTH) | | |
| 5. Thyroid stim. hormone (TSH) | | |
| 6. Somatotrophic hormone (STH) | | |

### b) Human Chorionic Gonadotrophin (HCG)

A list of protein hormones must include HCG, which is present in the urine and serum of pregnant subjects. HCG stems from the trophoblastic cells of the placenta.

This hormone was originally called Prolan and the anterior pituitary was thought to be its site of production. The hormone in pregnant mares' serum (PMS) has no chemical or biological relationships with HCG. HCG, unlike the gonadotrophic hormones of pituitary origin, can be obtained in fairly large amounts. In practice HCG, rather than anterior pituitary hormone, is used to stimulate gonadal function. Whether or not "human placental lactogen" (HPL) is a further, separate protein hormone is still under debate. It is said to have luteotrophic action.

## IV. Synthetic Substances with Hormone-like Actions

A certain number of synthetic substances have hormonal actions although their structure does not resemble naturally-occurring hormones. They are, in a sense, substitutes, and several oestrogens are important in this respect. Stilboestrol was the first to appear, and later substances were dienoestrol, hexoestrol, benzoestrol and allenolic acid. Paraoxypropiophenone, in spite of some contradictory evidence, is a weakly oestrogenic substance (with regard to its central and peripheral actions). Clomiphene, known to stimulate ovulation, also belongs to this group.

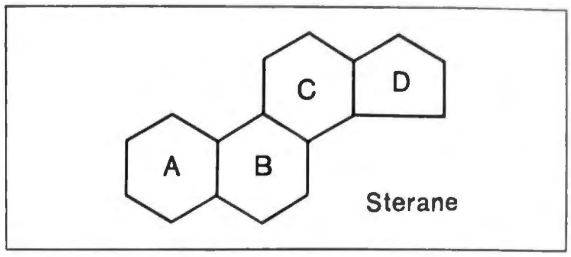
## V. Anti-hormones

'Anti-hormones' may be formed in circumstances where a protein hormone from one species is repeatedly injected into an animal from another species. The name 'anti-hormones' is misleading as it implies that these substances have hormonal action. In fact, 'anti-hormones' are antibodies against foreign proteins. The fact that antibodies can be raised against protein hormones forms the basis for quantitative immunological assays (see page 57). In humans, repeated injections of PMS or animal pituitary extracts (over a period of at least 1 month) lead to 'anti-hormone' production, which diminishes the therapeutic action of the substances injected. It is said that after an interval of 3—6 months without treatment, antibodies can no longer be detected. HCG extracted from human pregnancy urine, does not lead to antibody formation when injected into humans.

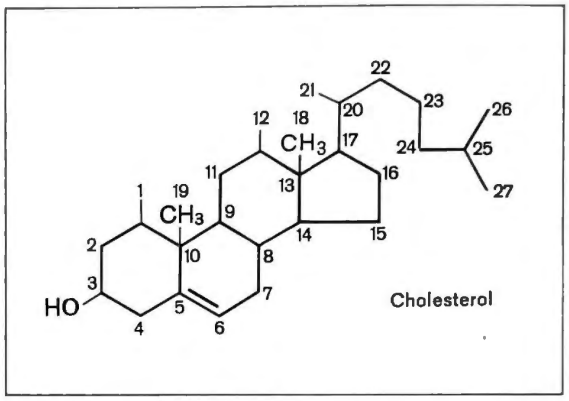
# B. Chemistry of Hormones

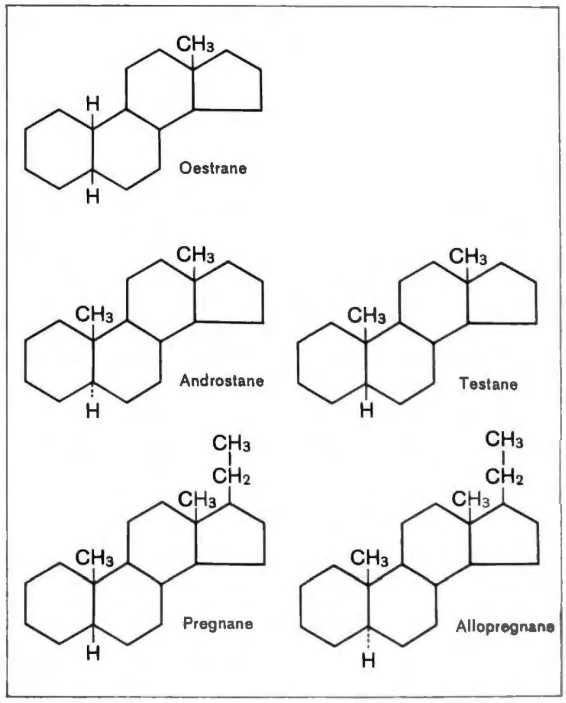
## I. Steroid Hormones

All steroid hormones have a cyclopentanophenanthrene (Sterane) ring.




Rings A, B and C each have 6 carbon atoms while ring D has 5. The way in which the carbon atoms are numbered can be seen by studying the illustrated structure of cholesterol from which all steroid hormones are formed.



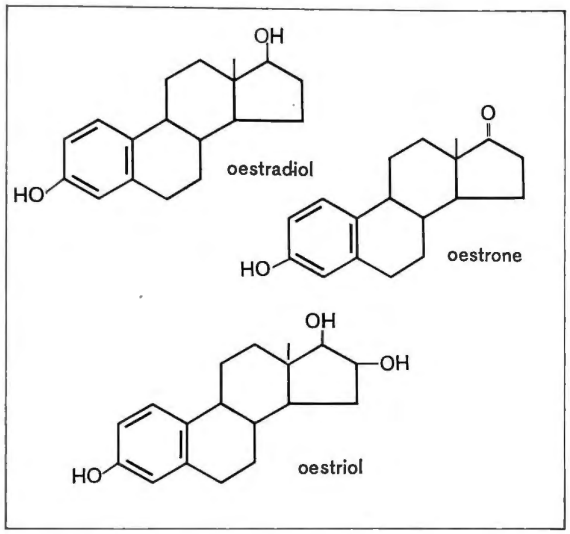




Except for oestrogens and aldosterone, all naturally occurring steroids possess methyl groups attached to carbon atoms 10 and 13.

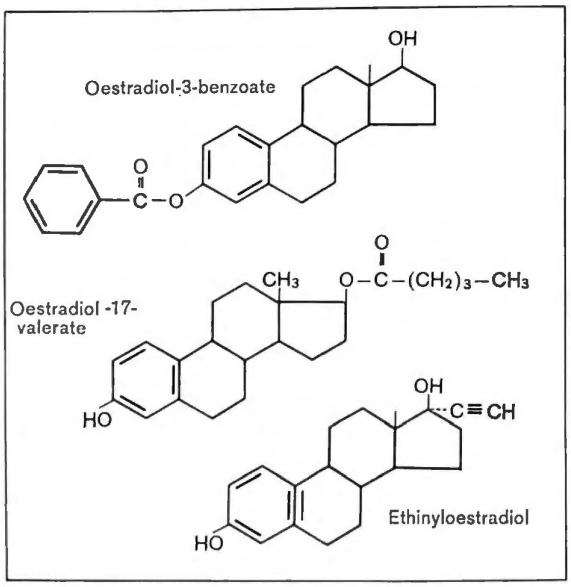
For the sake of simplicity, the chemical symbols for the methyl groups are omitted, but their presence is indicated by a vertical line. According to the number of carbon atoms they possess, we recognise $C_{18}$ steroids (oestrone derivatives), $C_{19}$ steroids (androstane and testane derivatives) and $C_{21}$ steroids (pregnane and allopregnane derivatives).

### a) Oestrogens

These are oestrone ($C_{18}$) derivatives. They are characterised by an aromatic A ring, the absence of a methyl group at $C_{10}$ and a hydroxyl group at $C_3$. Of the three naturally occurring oestrogens, oestradiol is the most active. Oestrone and oestriol, which are derivatives of oestradiol and are excreted in the urine, are less active.

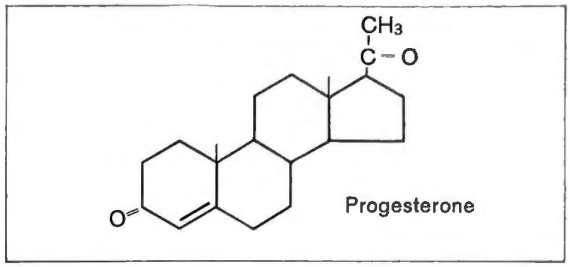



Oestradiol benzoate, oestradiol valerate (a depot form) and orally active ethinyl oestradiol are the substances of greatest importance in therapeutic use.

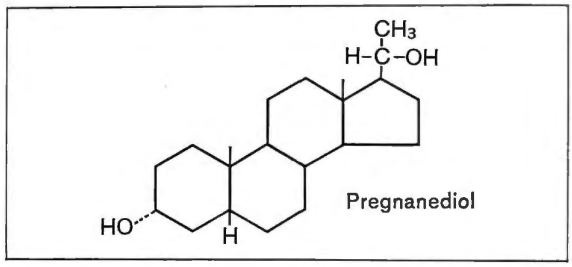



### b) Progestogens

The naturally occurring luteal hormone, progesterone, belongs to the large group of $C_{21}$ steroids which includes the adrenal hormones. This is not surprising as progesterone is not only found in the corpus luteum, but also occurs as an intermediary metabolite in the adrenal.




By a process of reduction, progesterone is converted into pregnanediol. Although the latter is inactive, its measurement in urine is of clinical interest.




Progesterone is sparingly soluble in oil, quickly broken down, and has no appreciable depot action. It thus does not satisfy the criteria demanded of hormones for modern clinical use.

It was found that oestradiol and testosterone could be rendered markedly progestogenic by esterification or introduction of an alkyl (methyl or ethinyl) group. An analogous modification of progesterone was not possible and for this reason the search for other progestational steroids began relatively early. It first led to the production of pregnenolone, an orally effective substance which has since become obsolete because of its relatively weak action. Many other progestational substances have been discovered in recent years and can be arranged, according to their structure, in 6 major groups.

I. Progesterone, retroprogesterone.
II. Derivatives of the 17-α-hydroxyprogesterone esters.

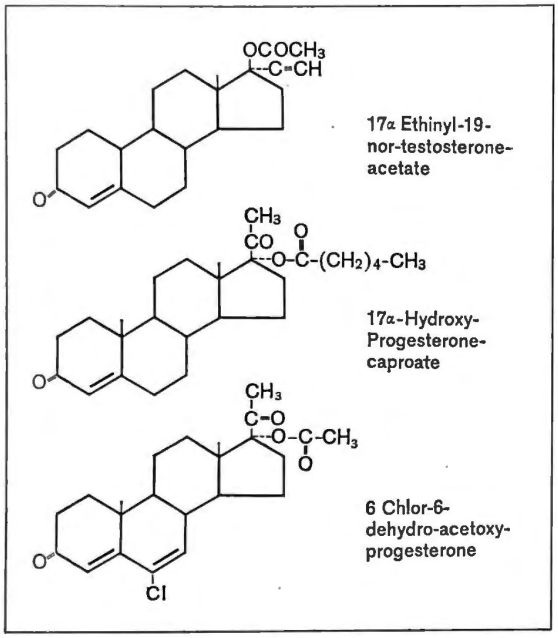
III. Derivatives of the 19-norhydroxyprogesterone ester.

IV. Derivatives of testosterone.

V. Derivatives of 19-nortestosterone.

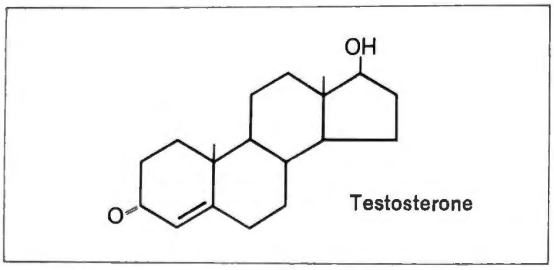
VI. Derivatives of deoxo-19-nortestosterone.

The progestational action and side effects of each group are different (see page 21). Substances of particular value in clinical use include 17-α-hydroxyprogesterone-caproate from group II (a depot progestogen), 17-α-ethinyl-19-nortestosterone-acetate from group V (tablets) and 6-chlor-6-dehydro-acetoxy-progesterone from group II (tablets).




## c) Androgens

The androgens are $C_{19}$ steroids. Testosterone, the naturally occurring male sex hormone, is characterised by a hydroxyl group at $C_{17}$.

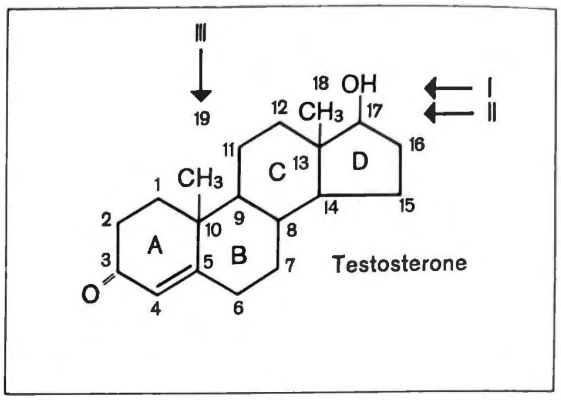



Using testosterone as a starting material, a number of substances with characteristic actions have been synthesised.

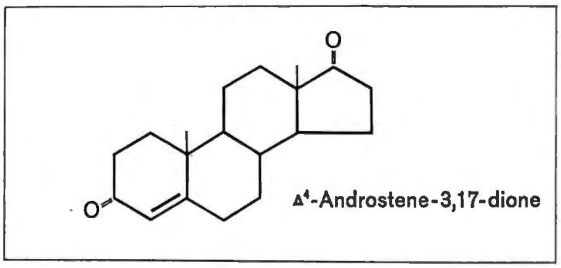
1. Esterification with propionic or oenanthic acids (arrow I) led to the production of potent androgens with varying durations of action.

2. The addition of a methyl group at $C_{17}$ (arrow II) led to the synthesis of an orally active androgen, methyl testosterone.

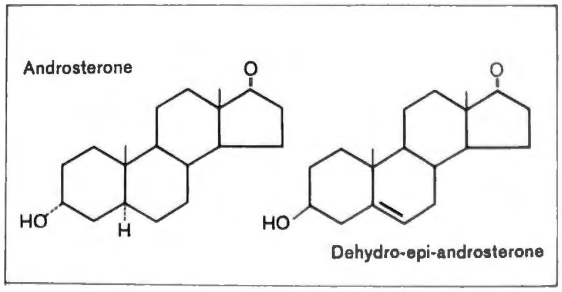
3. By the addition of an ethinyl group at $C_{17}$ and removal of the methyl group at $C_{19}$, the powerful progestational substance ethinyl-nortestosterone was obtained (arrow III).



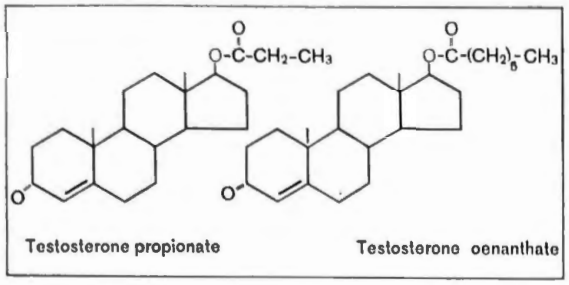

In the ovaries, adrenals and placenta, $\Delta^4$-androstene-3,17-dione, a substance closely related to testosterone is found. This substance is one of the 17-ketosteroids which are characterised by the conversion of the hydroxyl radical at $C_{17}$ into a ketone group.



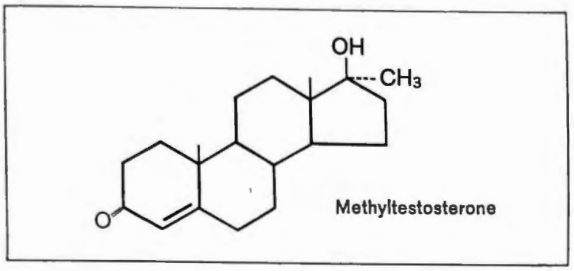

Numerous 17-ketosteroids are excreted in the urine. Most of them are derived from the breakdown of androgens formed in the adrenals. Androsterone (regarded as the excretory metabolite of the gonads) and dehydro-epi-androsterone (an adrenal metabolite) are substances particularly worth mentioning in this group.



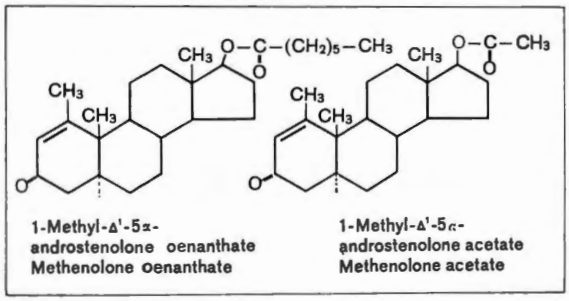
In clinical practice a number of substances are employed for their androgenic effect. They differ either in their method of use, or in their relative androgenic and progestational actions. Testosterone esters include:




Methyltestosterone is used orally.

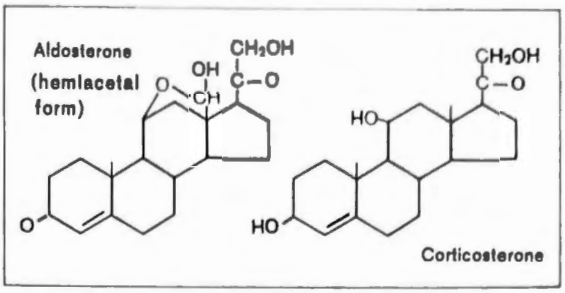



The related substance, ethinyltestosterone, has already been mentioned as a weak progestogen. Androgens with a weak sex-specific action and a powerful anabolic effect on protein metabolism are known as anabolic hormones.



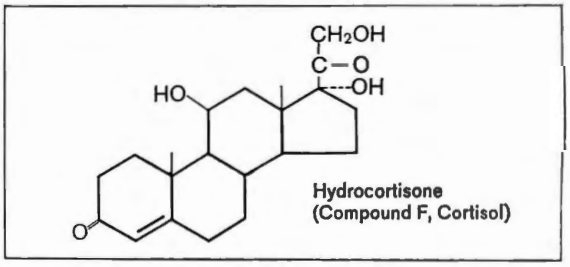

### d) Mineralocorticoids and Glucocorticoids

The adrenal hormones are classified, according to their action, as mineralocorticoids, glucocorticoids or androgens. The chemical structure of the $C_{21}$ gluco- and mineralocorticoids is characterised by an extra OH group at $C_{21}$. This constitutes a so-called α-ketol side chain. Aldosterone acts like a mineralocorticoid with respect to its effect on $Na^+$ and $K^+$ balance. Corticosterone, formerly regarded as the naturally occurring mineralocorticoid, is now thought to be an intermediary metabolite in aldosterone synthesis.




Therapeutically, deoxycorticosterone acetate is the most important substance. Its value in keeping patients with *Addison's* disease alive has long been recognised.

Glucocorticoids have, in addition to an α-ketol side chain, a 17-α-hydroxyl (OH) group as well as an oxygen atom at C 11. Their effect on mesenchymal tissues has led to their widespread clinical use. The most important naturally occurring steroid in this group is hydrocortisone.

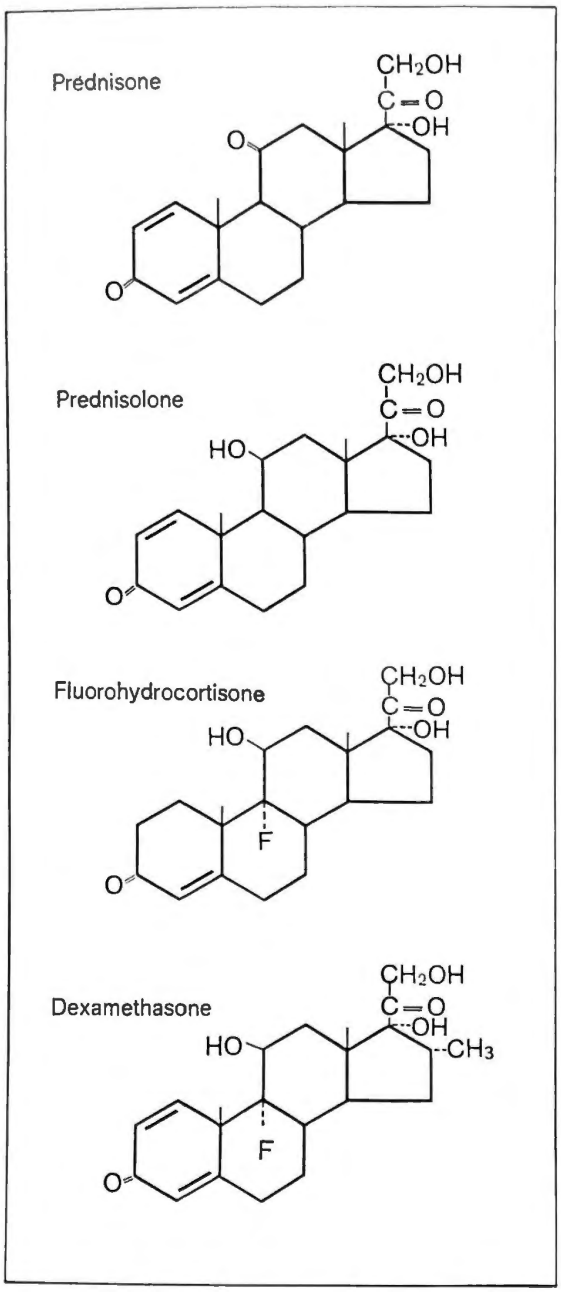



It is important to appreciate that glucocorticoids are not only excreted in reduced form as 17-hydroxycorticoids or 11-oxycorticoids, but also as 17-ketosteroids. The search for potent glucocorticoids which can be administered without undesirable side effects has led to the discovery of further compounds, notably prednisone.

## II. Protein Hormones

Our knowledge about the chemical structure of protein hormones is still incomplete. They are all water soluble and are composed of large numbers of amino-acids. FSH, ICSH and TSH also contain carbohydrate and are known as glycoproteins. The molecular weight of protein hormones ranges from 1000 (oxytocin and vasopressin) to 40,000 (FSH and ICSH). The chemical structure of vasopressin, oxytocin and ACTH are known and their synthesis is possible. With the exception of insulin, the detailed structure of all other protein hormones is not yet known. Differences between hormones can be detected by

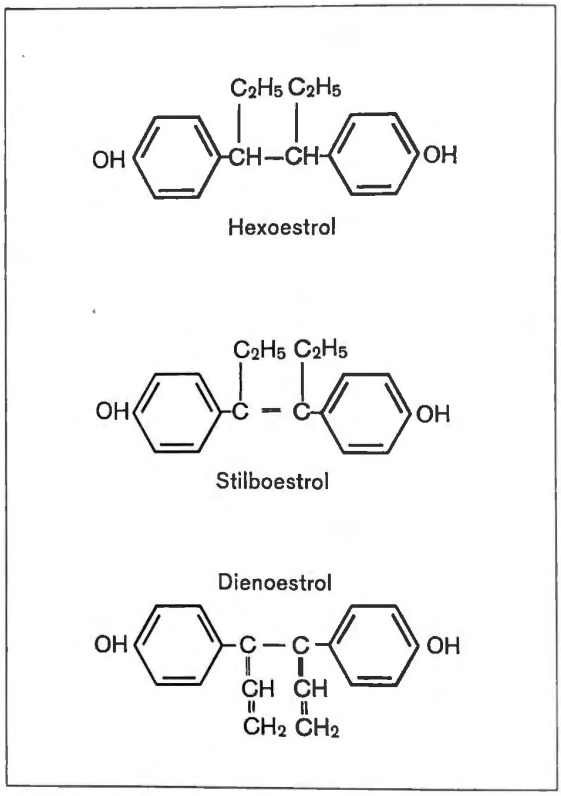
physico-chemical means, e. g. chromatography, molecular weight determinations and the effect of certain enzymes.



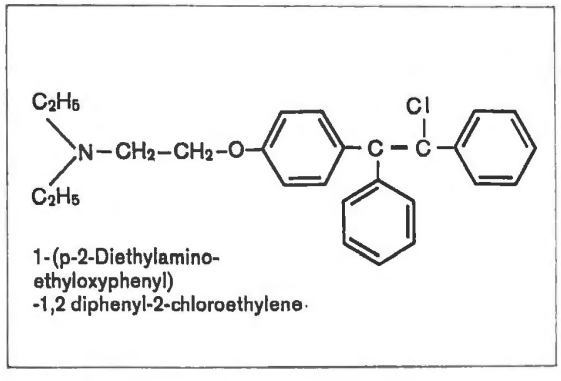

The chemical analysis of high molecular weight protein hormones is rather complicated. With regard to synthesis, the bonds between carbohydrate and protein present particular difficulties. The differences between trophic hormones from animal and human sources also present problems. Growth hormone from animal sources has, for example, no effect on the human being. In molecular weight (about 20,000) and immunological properties, it resembles prolactin (LTH). A relatively large amount of gonadotrophic hormones can be isolated from human menopausal urine and is known as HMG (human menopausal gonadotrophin). HMG is a mixture of FSH and ICSH. Because of their protein nature, human chorionic gonadotrophin (HCG) extracted from pregnancy urine and the hormone in pregnant mares' serum (PMS) belong to this group. Their exact chemical structure is unknown. HCG and PMS are glycoproteins.

## III. Synthetic Non-Steroid Oestrogens

The most important non-steroidal oestrogens are derivatives of stilbene. The symmetry of their structure is seen by studying their formulae.




Clomiphene also belongs to this group. It is related to a synthetic oestrogen and stimulates ovulation. Its formula is as follows:



# C. Origin, Synthesis and Breakdown of Hormones

## I. Steroid Hormones

### a) Site of Production

The many publications covering the extraction of steroids from endocrine glands show that their steroid hormone content is relatively small. An appreciable storage of steroids does not seem to occur. The amounts of hormone recovered do not, therefore, reflect the amount of hormone produced. One should also not regard every steroid recovered from an endocrine gland as one of its secretions, as intermediary metabolites as well as definitive end-products are obtained by extraction.

*Oestrogens* have been found in all the glands in which steroids are formed. Oestradiol has been identified in the ovaries, placenta and testes, and oestrone in the adrenals. Oestriol is mainly found as an excretory metabolite in urine. Oestradiol from the ovary is probably produced in the Graafian follicles and the corpus luteum. The theca cells and granulosa cells are involved in their production.

In addition to the 3 'conventional' oestrogens, a number of related steroids have been identified in tissues and urine in recent years. These are probably oestrogen metabolites (16-epi-oestriol, 16-α-hydroxyoestrone, 16-oxo-17-β-oestradiol, 16-β-hydroxyoestrone, 2-methoxyoestrone, 2-methoxyoestriol).

Progesterone, the most important *progestogen*, can be identified chemically in the mature follicle or in the corpus luteum. It is formed by the granulosa cells. Progesterone has likewise been found in the placenta. Another progestogen, progesterol-20 α has been found in human ovaries. The pregnanediol which is found in urine at times other than the luteal phase of the cycle stems from the adrenals.

*Androgens*, like oestrogens, are found in all the endocrine glands in which steroids are formed. The androgenic compound isolated from the testes, the ovaries and the adrenals is $\Delta^4$-androstene-3, 17-dione. Testosterone has so far been found only in the male gonads. It is thought that the ovarian androgens are produced by the interstitial and hilar cells.

The amount of androgens produced by the ovary can be estimated by comparing their 24-hour urinary excretion in normal and castrated women. Their chemical structure and biological activity cannot be deduced from such measurements. The zona reticularis cells of the adrenal are probably the main site of androgen production.

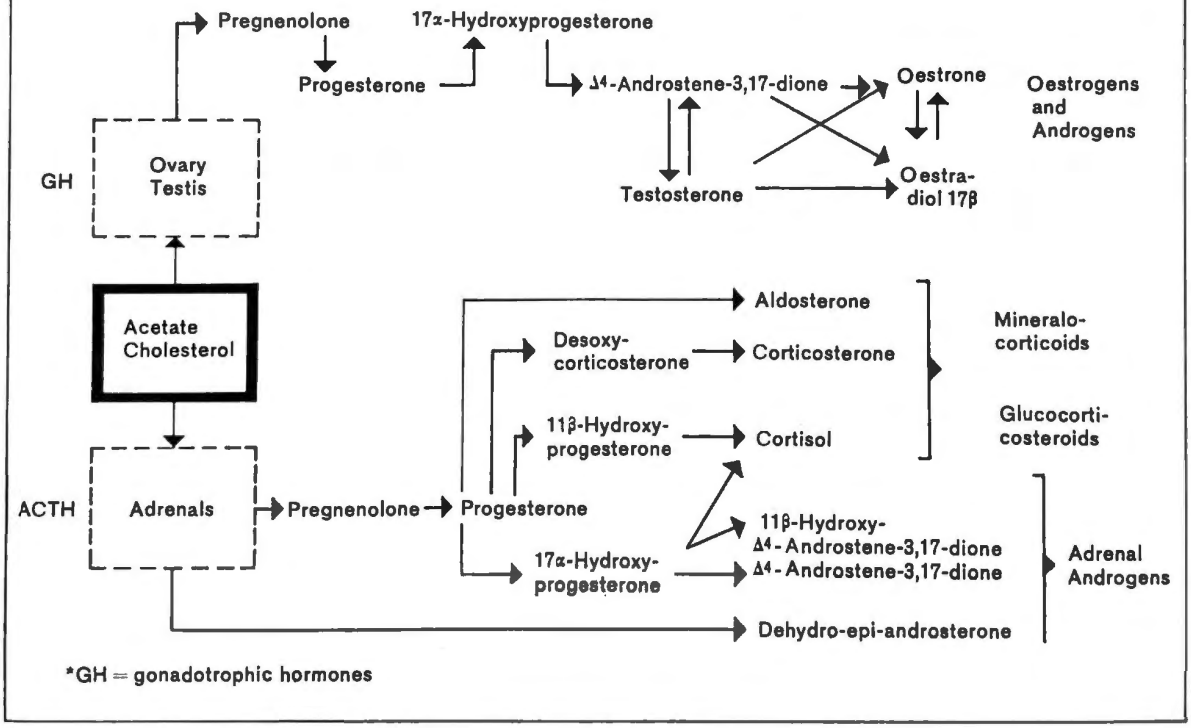
In non-pregnant women, *gluco-* and *mineralocorticoids* are probably only produced in the adrenal. It is thought that dehydrocortisone is formed by the zona fasciculata cells and that aldosterone as well as deoxycorticosterone come from the zona glomerulosa.
Observations on pregnant women with *Addison's* disease and studies on experimental animals which are hypophysectomised during pregnancy suggest that the placenta can also synthesise adrenal hormones.

### b) Biosynthesis

The biosynthesis of steroid hormones is a specific function of the gonads, the adrenals and the placenta. The factors controlling this process are not known in complete detail. The individual chemical steps of biosynthesis have, in recent years, been studied in detail by perfusion and incubation experiments using labelled steroids. The particular ability to synthesise steroids seems to depend on the presence of a certain pattern of enzymes. This pattern seems very similar in the ovaries, the testes and the adrenals, embryologically all derived from the gonadal ridge. The large number of steps involved in synthesis demands that the number of specific enzyme systems is correspondingly numerous (e.g. hydroxylases, hydrogenases, dehydrogenases and desoxylases). Biosynthesis is further dependent on the presence of the corresponding trophic hormone. A deficiency of anterior pituitary function soon leads to disuse-atrophy of dependent endocrine glands. *Per contra*, overstimulation of dependent endocrine glands with trophic hormones from the anterior pituitary leads to increased production and secretion of peripheral hormones. Vitamin C, which is found in appreciable quantities in the adrenal and gonads, seems to have a catalytic action. Its quantitative measurement is used as a method of measuring gonadotrophic activity.
The basic substance required for hormone synthesis is cholesterol acetate. This substance is made in the liver, the muscles and other, non-endocrine sites. It is also ingested with a normal diet. There are several possible paths of steroid synthesis starting with cholesterol acetate, but the pathway illustrated in Table 3 is the one that is generally accepted. One of the first intermediary products in the gonads and adrenals is the biologically inactive sub-

Table 3.

Steroid hormone production in the endocrine glands
(Modified from Dorfman, R.I.: Amer. J. Med. 21, 679 [1956].)



stance, pregnenolone, from which progesterone is formed. Other steps, which in some cases are still a matter of conjecture, are given in bare outline in table 3. The synthesis of steroid hormones *in vivo* is a much more complex process than Table 3 suggests. It has not yet been proved that the biosynthesis of steroids from cholesterol and acetate can occur in the placenta. Perfusion experiments suggested the contrary. The central position of progesterone on the pathways of testosterone, oestradiol and adrenal-hormone synthesis is of particular interest.

The fact that the gonadal oestrogens are derived from androgens is also striking. All ovarian androgens are probably not used in this way which means that some may escape into the circulation. It is not at present certain whether $\Delta^4$-androstenedione, the only androgenic steroid recovered from the ovary, should be regarded as an individual hormone or as an intermediary metabolite in oestrogen synthesis.

Oestradiol and oestrone have been found in the ovary. These substances are therefore the true, naturally occurring oestrogens while oestriol is a secondary breakdown product.

There are a number of disorders caused by inadequate biosynthetic activity in endocrine glands.

**Examples:** I. The adrenal defect in the *adreno-genital syndrome* is basically a block of steroid synthesis at the progesterone or pregnenolone level.

II. In the *Stein-Leventhal syndrome*, the conversion of androgens into oestrogens in the ovary is disturbed.

### c) Breakdown and Excretion—Peripheral Regulatory Mechanisms

The breakdown and excretion of steroid hormones resembles their step-wise synthesis. The body is in a position to balance synthesis and breakdown by means of sensitive regulating mechanisms. Protection against excessive or deficient hormone levels is thus feasible.

In the blood, hormones either exist free or in a protein-bound state with attachments to the albumin and globulin fractions. The amount of circulating hormones is relatively small. Their detection in plasma is therefore difficult. By the bloodstream, the hormones reach their target organs, where their mode of action is still largely unknown. In addition, their solubility in fat may mean that they can be stored in fatty tissues.

The breakdown of hormones into inactive metabolites is mainly achieved in the liver which possesses the appropriate enzyme systems. There, the steroid hormones are made soluble in water by esterification with glucuronic or sulphuric acids. This formation of water-soluble substances is known as *conjugation.*

The processes here described are part of the *peripheral regulating system* to which a number of organs contribute: the gonads (site of breakdown or chemical modification of hormones), the liver (site of degradation and transformation of hormones), the blood (transport medium) and the kidneys (excretory organs). Fat, a solvent and hence a depot for steroid hormones, has an effect on distribution and excretion. This regulating mechanism complements the control which the hypothalamic/pituitary system exerts over the peripheral endocrine glands and together they achieve an adequate hormonal balance. The breakdown and inactivation of hormones in the liver depends on a number of factors.

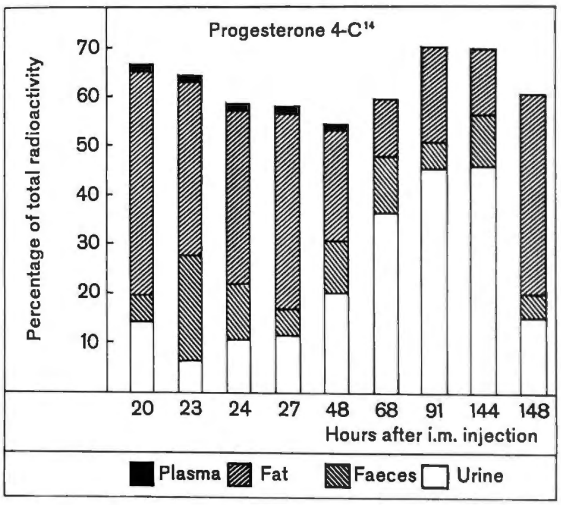



Figure 1. Distribution of labelled progesterone or its metabolites.
(*Plotz, E. J.*: 6. Symposion der Deutschen Gesellschaft für Endokrinologie, Springer-Verlag 1960, S. 25).

A liver affected by degenerative disease or toxic agents is unable to metabolise steroid hormones normally. Vitamin B deficiency has the same effect. Clinical observation suggests that the inactivation of oestrogens is particularly affected by liver disease. This leads to an accumulation of hormones produced by the Graafian follicle (a "hepatogenic hyper-

follicular state"). As a result, one finds that some men with cirrhosis show signs of feminisation, while women occasionally develop menstrual upsets.

In a healthy subject, the time required for inactivation of steroids is very short. At the end of pregnancy, the placenta has to replace all the circulating progesterone every 3.3 minutes or so, in order to maintain physiological concentrations of this hormone. This interval is known as the "turnover time". Esterified steroids dissolved in oil are excreted more slowly (see page 44).

The water-soluble, conjugated steroids are excreted by the kidneys, and also into the intestine via the biliary tract. There is considerable species variation in the proportion of excretory metabolites found in urine and bile. In human beings, this proportion is probably also subject to considerable individual variations. Clinical observations and animal experiments suggest that some of the steroids excreted into bile are reabsorbed in the intestine. There is thus an "enterohepatic circuit", even in man (figure 2). Expiratory air, sweat and desquamated skin may also constitute routes of excretion.

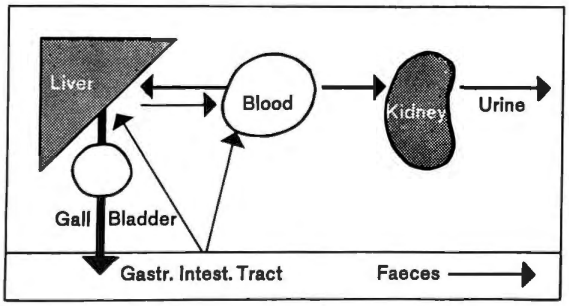



Figure 2. Enterohepatic circulation of oestrogens. (*Sandberg, A.*, a. *Slaunwhite, M. R.*: J. Clin. Invest. **36**, 1266 [1957])

The steroids excreted in urine can be divided into chemical groups. Further separation into individual metabolites can also be achieved (e.g. by chromatography).

Only limited deductions about the range of hormone production can be made from measurements on urine as they provide no information about the hormone excreted into the bile, nor do they account for the non-steroid breakdown-products of steroid hormones.

If, for example, labelled oestradiol is injected, 80% of its radioactivity is recovered in urine. The quantitative chemical measurement of the 3 commonest metabolites, however, only gives a 30% recovery.

Table 4.

| Oestrogens detectable in human urine |
|---|
| 1. Oestrogens<br>17β-Oestradiol, Oestrone |
| 2. Metabolites<br>Oestriol, 16-Epioestriol, 16,17-Epioestriol, 17-Epioestriol, 16α-Hydroxyoestrone, 16β-Hydroxyoestrone, 16-Ketooestrone, 16-Keto-17β-oestradiol, 6-Hydroxyoestrone, 2-Methoxyoestrone, 2-Methoxyoestradiol, 2-Methoxyoestriol, 18-Hydroxyoestrone, 11β-Hydroxy-17β-Oestradiol, Equilenine, Oestranediol A and B |

The site of origin of urinary steroids is also difficult to determine. Oestrogens come not only from the ovaries but also, in small amounts, from the adrenals. Certain androgens in therapeutic use may be partly excreted as oestrogens. It has been found that of the pregnanediol in urine, 1 mg. a day comes from the progesterone produced in the adrenals. Only briefly, during the life span of the corpus luteum, does the pregnanediol in urine come from progesterone formed in the ovary. Conclusions about the origin of 17-ketosteroids in urine are particularly difficult. The majority come from the adrenals, androgens and some glucocorticoids being excreted in this form. A small fraction of the 17-ketosteroids excreted stems from the ovaries. Through measurements of the 11-oxysteroids and the 17-ketogenic steroids it is possible to obtain a much clearer picture of the adrenal metabolites in urine.

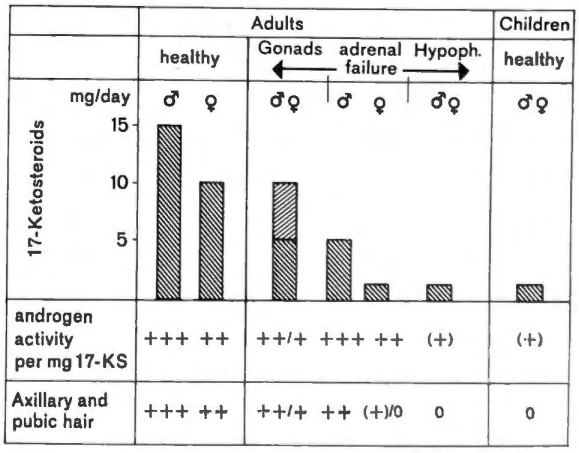



Figure 3. Daily excretion and androgen activity of 17-Ketosteroids in subjects, who are healthy or suffering from various types of endocrine failure. (*Prader, A.*: Mschr. Kinderhk. **104**, 157 [1956])

In pregnancy, the oestrogens and pregnanediol found in urine almost all come from the placenta.

## II. Gonadotrophic Hormones

### a) Origin

In addition to growth hormone, ACTH and thyrotrophic hormone, FSH, ICSH and LTH are formed in the anterior pituitary. The cells from which each hormone is derived have not been identified with certainty.

The number of hormones produced exceeds the types of cell identified by specific staining techniques. There are two theories about the cells seen in sections of the anterior pituitary:

1. *The "single cell type" Theory:* This states that a single cell type is responsible for the production of all anterior pituitary hormones. The supporters of this theory claim that the variable staining characteristics of the cells in the anterior pituitary represent variable maturity of function.

2. *The "multiple cell type" Theory:* According to this theory, there are distinct cell types with individual staining characteristics. Thus, it is claimed that LTH and growth hormone come from the acidophil cells, while FSH, ICSH and thyrotrophic hormone (all proteins containing carbohydrate) are all said to come from the "glycoprotein-positive" basophil cells.

Oxytocin is not, as previously thought, formed in the posterior pituitary, but comes from the supra-optic nucleus in the midbrain. From there, it is transferred to the posterior pituitary, whence it is released by certain stimuli.

In pregnancy, the placenta becomes the site of gonadotrophic hormone production. Large amounts of chorionic gonadotrophin are produced by the trophoblastic cells which are identifiable from a very early stage of embryonic life.

In the animal kingdom, a gonadotrophic hormone (PMS) which is found in pregnant mares' serum between the 60th and 120th days of gestation is of particular importance. This hormone is probably also formed by chorionic tissue.

### b) Biosynthesis and Breakdown

Only a limited amount of information is available about the formation and breakdown of protein hormones. A large number of amino acids and their conjugation with carbohydrates are definite requirements for their synthesis. The gonadotrophin content of the anterior pituitary is relatively small. Thyrotrophic hormone and ACTH are present in larger amounts.

The distribution of anterior pituitary hormones in the body has been followed by using labelled protein hormones. Prolactin, for example, accumulates in the ovary and in the ventral lobe of the prostate. The gonadotrophic hormones are almost certainly only partly excreted in urine. In clinical experiments, only 10% of the hormone injected was recovered in its biologically active form in urine.

The situation with PMS is different. Neither a mare nor treated humans excrete this hormone in urine. It is probable that it is broken down into small, inactive components.

# D. Control of Gonadal Function and Central Regulatory Mechanisms

The gonads, like other endocrine glands, are under the influence of a "neuro-hormonal" regulating mechanism which influences the production of steroid hormones and protects the body from their excessive or deficient secretion.

This control is mediated by the hypothalamus and anterior pituitary whose functions are themselves dependent on secretions from the glands they control. Deficient anterior pituitary function leads to atrophy of the dependent endocrine glands. Deficient or absent function of the gonads, adrenals or thyroid leads, in turn, to increased production of the respective trophic hormones by the anterior pituitary with corresponding morphological changes. In this way, central mechanisms try to compensate for peripheral hormone deficiencies.

A special relationship exists between the anterior pituitary and the ovaries. Because processes such as ripening of the follicle, ovulation and corpus luteum formation are dependent on gonadotrophic hormones, the latter hormones regulate not only the quantitative output of ovarian hormones but also the timing of their release. The ovarian steroids act on the "sex" centre in the midbrain. In the anterior part of the hypothalamus, certain substances which stimulate the production of gonadotrophic hormones are formed. These substances are known as "releasing factors". Chemically they are polypeptides with a molecular weight around 3,000 and their structure is thus more like that of vasopressin than of the complex pituitary hormones. The "releasing factors" reach the anterior pituitary through the infundibulum or via the portal-hypophyseal circulation. "Releasing factors", unlike trophic hormones, are not species-specific. This has been shown for ICSH and its corresponding "releasing factor". Experiments with ablation of certain hypothalamic centres suggest that there are areas which depress rather than stimulate the release of gonadotrophins. It is thus obvious that there is a "neurohormonal circuit" whose three components, the ovaries, midbrain and anterior pituitary, must be intact for normal menstrual function. This regulatory mechanism which exists between peripheral endocrine glands and their controlling centres has also been known as the "*cybernetic principle*" or "*feed-back mechanism*".

It is probable that the stepwise sequence of events is as follows: FSH leads to the ripening

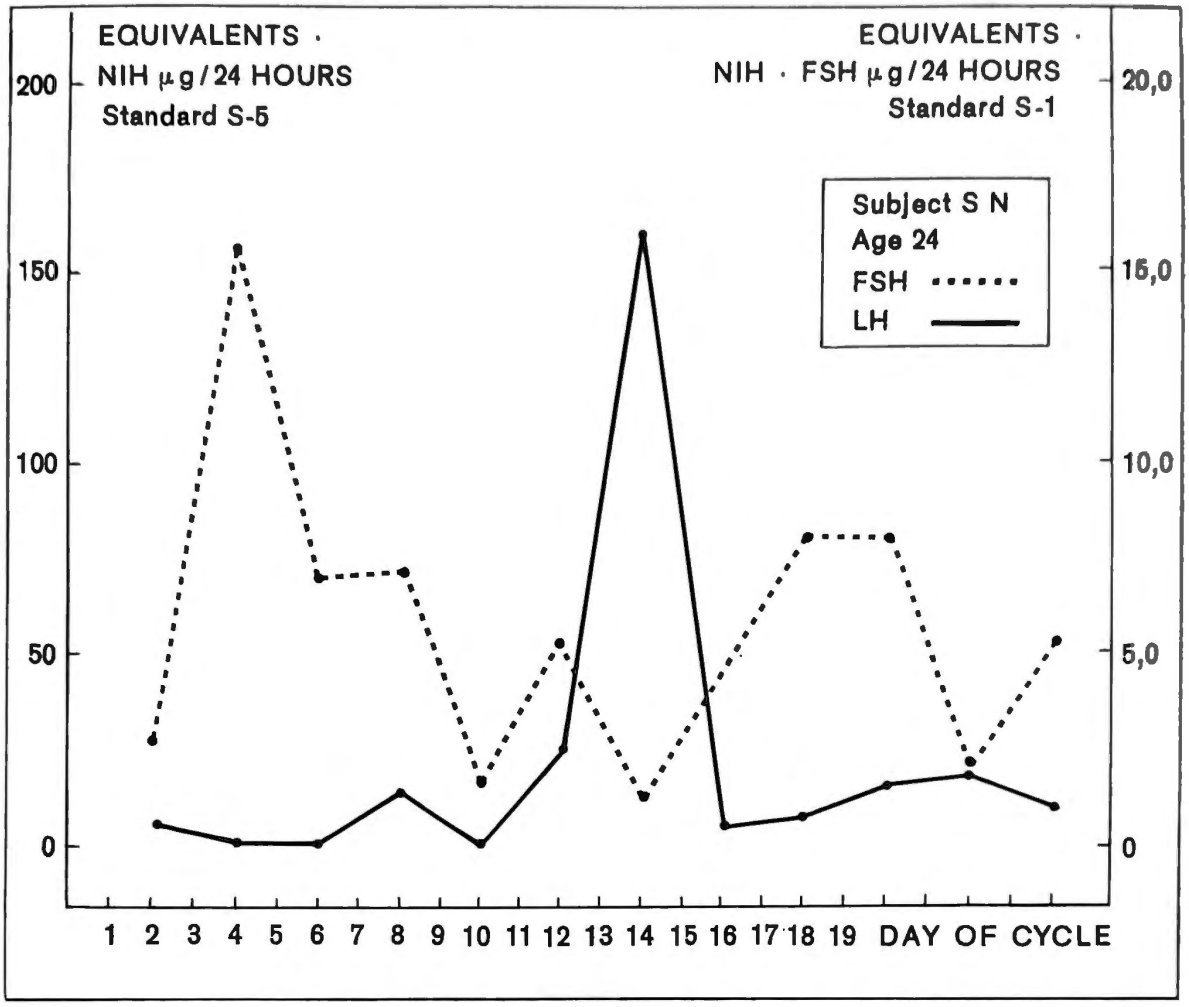



Figure 4. Relationship of FSH - - - and ICSH —— excretion patterns in a normal 24-year old woman (*Fukushima, M.* et al.: J. clin. Endocr. 24, 2, 205 (1964).

of a follicle, and later, in combination with LH (or ICSH) from the anterior pituitary to maturation of the follicle with oestrogen secretions.
The increasing oestrogen output from the ovaries leads to a suppression of FSH production while the amount of LH formed increases. As soon as follicular rupture (a process which is apparently dependent on the FSH/LH ratio) occurs, the output of luteotrophic hormone begins to increase while progesterone from the corpus luteum suppresses LH secretion by the anterior pituitary. This concept is by no means generally accepted. It is worth noting that serial measurements of the 24 hour excretion of the 3 gonadotrophic hormones present considerable difficulties. The following points require further study:

I. FSH levels during the follicular phase (figure 4).

II. Prolactin levels (figure 6).

III. The significance of androgen production by the ovaries.

IV. The effect of progesterone on hypothalamic/anterior pituitary balance.

The factors involved in endocrine balance appear to be more complex than our present-day concepts. There is little doubt, for example, that there is an inter-relationship between peripheral endocrine glands which is either a direct one or is mediated through the hypophyseal-hypothalamic axis.
It is thus not surprising that a disorder of one endocrine gland results in disturbances in others.

**Example I:** Hyperthyroidism is not uncommon in the climacterium. It is thought that this is the result of a disorder in the hypothalamic-anterior pituitary axis. The anterior pituitary apparently reacts to a cessation of ovarian function not only with an increased production of gonadotrophins but also with an increase in the formation of thyrotrophic hormone.

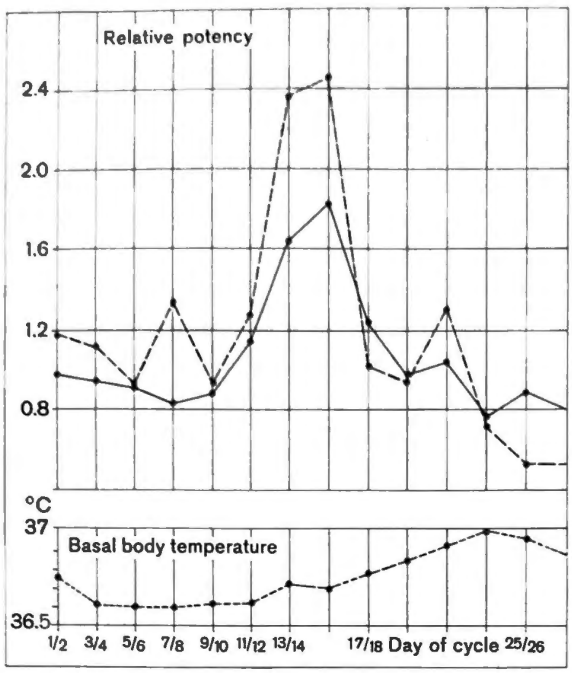



Figure 5. Total gonadotrophin (.- - -.) and ICSH (.——.) activities in 48 hour urine samples collected during the menstrual cycle.
(*Buchholz, R.*: Zschr. exper. Med. **128**, 219 [1957])

**II:** In sexually mature women, menstrual disturbances which are apparently resistant to therapy, may resolve spontaneously after treatment directed at an adjustment in thyroid function. This may be due to the effect such treatment has on the hypothalamic-anterior pituitary system.

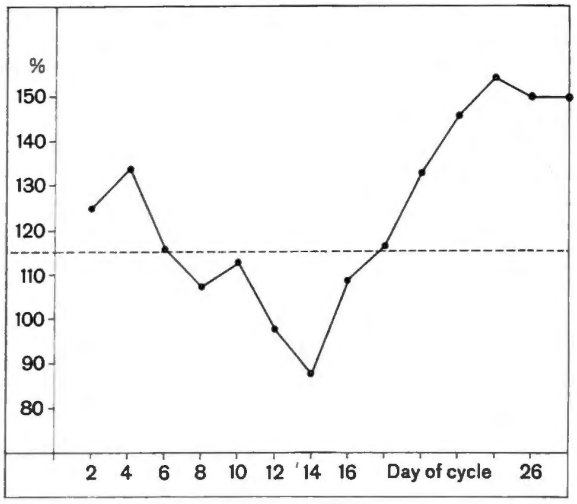



Figure 6. Blood prolactin content measured by pigeon crop method.
(*Simkin, B.*, and *Arce, R.*: Proc. Soc. Exper. Biol. Med. **113**, 485 [1963])

The relationship between adrenal and gonadal function becomes obvious with castration or in circumstances where there is hyperfunction of the adrenals. A biphasic menstrual cycle is hardly ever found in patients with the adrenogenital syndrome (excessive androgen production) or *Cushings'* disease (excessive glucocorticoid production). In experimental animals in particular, castration leads to adrenal hyperfunction. Again, it is probably the hypothalamic-anterior pituitary mechanism that is responsible for these effects.

An attempt has been made to explain the relationship between the gonads and the adrenal by a "shift-phenomenon". This concept states that the anterior pituitary cells have a finite functional capacity so that an increase in production of ACTH leads to a decrease in the production of gonadotrophic hormone (or vice-versa), while an increased production of both types of hormone is not possible.

There is also a possibility, as yet not proven, that the sex steroids have a direct inhibitory effect on the gonads. With this hypothesis, a high level of circulating steroids would render the gonads resistant to stimulation by gonadotrophic hormones, while a fall in steroid levels would make them more sensitive to the effect of gonadotrophins.

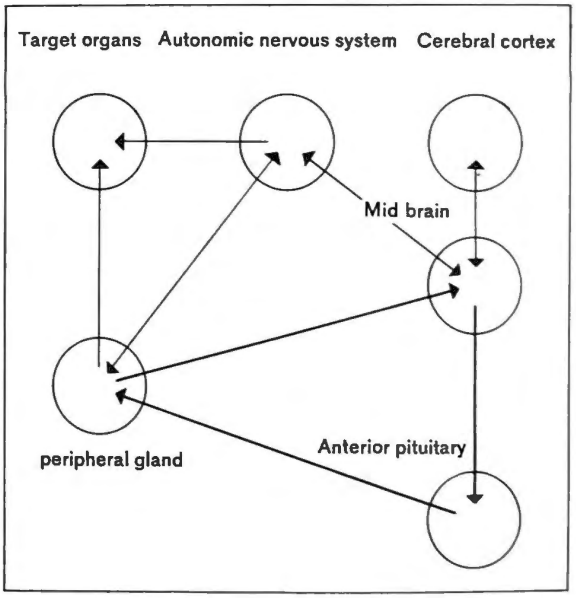



Figure 7. Scheme illustrating pathways of neurohormonal control.

Other influences which must be considered here are the effect of the autonomic nervous system on the endocrine glands and their target organs. In addition, it should be remembered that the cerebral cortex can influence the endocrine glands through its potential effect on the hypothalamus and anterior pituitary.

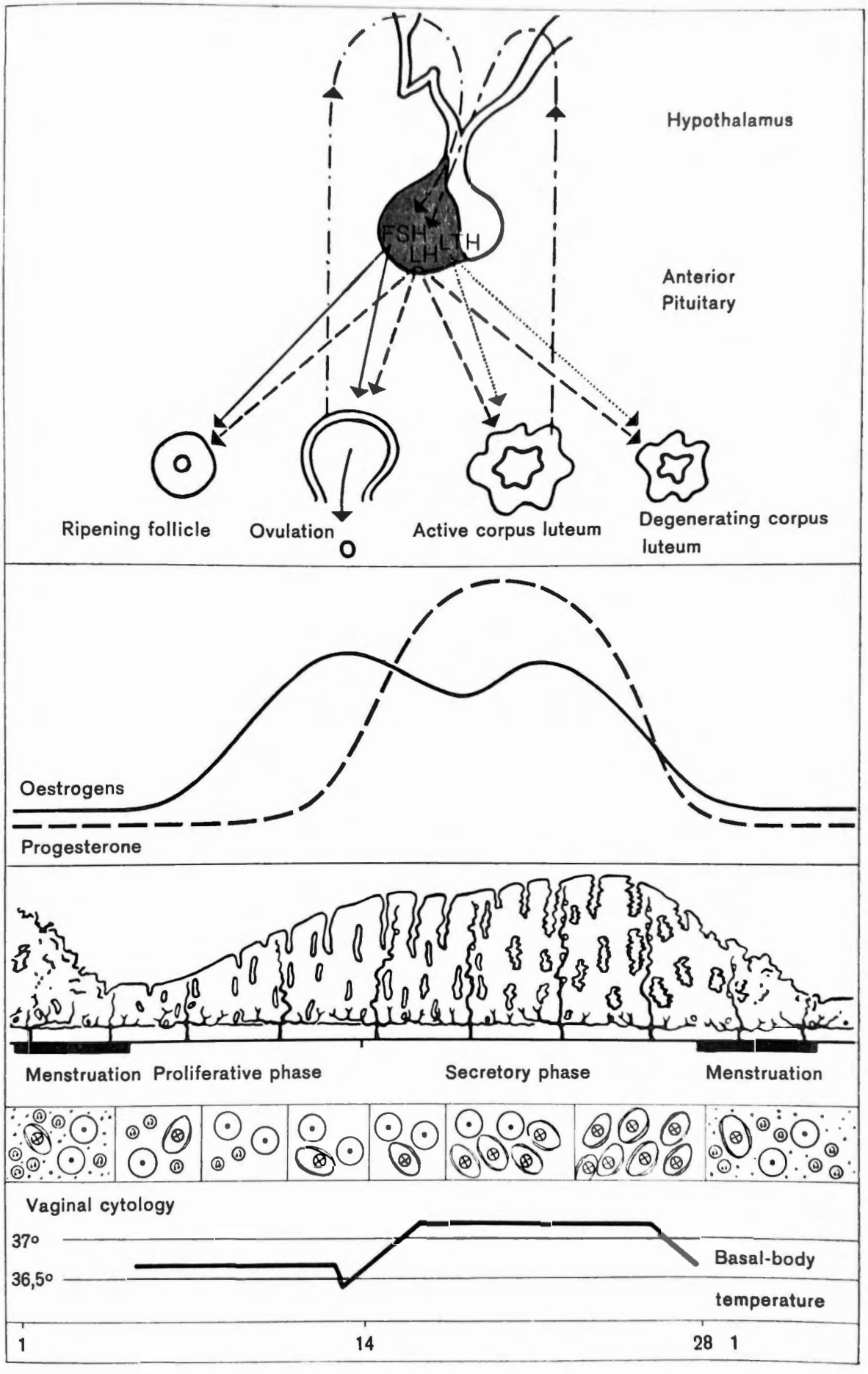



Figure 8. Relations between hypothalamic anterior pituitary system, ovaries, endometrium, vaginal changes and basal body temperature (*Pschyrembel, W.*: Praktische Gynäkologie Berlin 1964).

# E. Action of Hormones

## I. General Remarks

Our knowledge about the action of hormones started with the classical experiments of *Berthold*. The alterations which followed extirpation of a gland were noted and attempts were made to correct them by transplants or injections of extracts from the glands excised. The principles governing the regulation of endocrine glands were later studied in hypophysectomised animals, by experiments with parabiotic animals and by intra-splenic transplants of endocrine glands. Once the synthesis and structure of steroid hormones had been elucidated, it was possible to be more certain about the action of different groups of hormones.

Information about the manner in which hormones act upon their target organs is still scanty. The small quantity of hormones which reaches cells implies that hormones act in a catalytic manner and are neither sources of energy nor starting substances for biosynthetic processes. In this way they resemble the roles played by vitamins and enzymes. The difference between the latter substances and hormones lies more in their site of production than in their mode of action. It is likely that the peripheral action of hormones is achieved in several ways:

1. Intra-cellular effect on various enzyme actions.

2. Alteration in ionic and gaseous exchanges caused by changing the permeability of the cell membrane.

3. A direct action on the deoxyribonucleic acid (DNA) in the cell nucleus.

*In favour of 1.* Many cell proteins are of an enzyme nature. These enzyme systems are receptive to hormonal influences which can thus affect metabolism within the cell itself (e.g. its water content, its electrolyte balance and its protein synthesis). The latter changes may, in turn, bring about histologically recognisable alterations (proliferative endometrium, secretory endometrium or the appearance of spiral arteries).

*In favour of 2.* Hormones can probably change the permeability of cells in certain organs.

*In favour of 3.* A direct action of hormones on nuclear DNA has only been shown with ecdyson in insects. As a result, ribo-nucleic acid, a critical substance in protein synthesis, is activated. This mechanism may operate with sex hormones.

The effect of hormones is undoubtedly more complex than the above descriptions suggest. The autonomic nervous system also plays a role. An increased perfusion of tissue not dependent on hormonal influences may, of itself, cause alterations.

It is striking that the complex changes which normally only occur in response to specific hormones or their derivatives, may be produced by unrelated chemical substances. As examples, stilboestrol, hexoestrol, etc. have the same oestrogenic action as the naturally occurring follicular hormone. It might be added that many steroids have an effect which is synergistic with or antagonistic to the action of other steroids.

## II. Influence of Steroid Hormones on Metabolic Processes

The sex steroids, like the adrenal hormones, have general effects which have little connection with their specific effect on the genital tract. A study of the target organs after gonadectomy or with administration of certain hormones can provide information about the "primary action" of hormones. In this account, their "primary reactions" cannot be analysed in detail.

In the first instance steroid hormones have an effect on metabolic processes. Gonadal and adrenal androgens have an anabolic effect on protein metabolism. Testosterone administration leads to weight increase and decreased nitrogen excretion. This weight increase is most marked in striated muscle (myotropic action), heart muscle, and in parenchymal organs such as the liver and kidney (renotropic action). Protein storage occurs not only in cells but also in mesenchymal tissue—e.g. in bone matrix or in the tissue of a cock's comb.

The anabolic action of androgens which results in sturdy musculature and skeletal build, physiological in men, is pathological in women with the adrenogenital syndrome.

In clinical practice, the anabolic effect of androgens is frequently exploited. In many types of protein deficiency, testosterone and its esters, or the so-called anabolic steroids (weak androgens with a strong anabolic action) are often used with good effect.

In contrast to androgens, oestrogens and progesterone have little effect on protein metabolism.

Glucocorticoids oppose the effect of androgens on protein metabolism. Whether this is due to increased catabolism (catabolic action) or decreased anabolism (anti-anabolic action) has not yet been decided. In isolated instances, cortisone has been shown to increase the excretion of amino-acids, creatine and uric acid while it leads to a protein deficiency in certain tissues.

Cushing's syndrome, with its characteristic muscle wasting and osteoporosis is a clinical example of excessive glucocorticoid action.

Glucocorticoids mainly affect carbohydrate metabolism. Under certain circumstances, oestrogens and androgens can have the same effect.

Cortisone promotes the synthesis of carbohydrates by the mobilisation and increased breakdown of fat and proteins. It also increases the deposition of glycogen in the liver and muscles. High doses of cortisone can precipitate diabetes in a predisposed patient. In mild cases of diabetes, androgens and oestrogens can increase carbohydrate tolerance with a return of blood sugar to normal levels. In cases of juvenile diabetes which are insulin resistant, better control may be achieved by treatment with anabolic steroids.

There is only a limited inter-relationship between steroid hormones and fat metabolism. The obesity which often follows gonadal failure is probably of central origin. It is only slightly affected by sex hormones as they have a restricted effect on oxygen consumption of adipose tissue.

There is evidence to suggest that sex hormones can influence cholesterol and lipid metabolism. There is a rise of plasma lipids and cholesterol after oophorectomy which can be countered by the administration of oestrogens. A number of experimental studies suggest that raised cholesterol and lipid values are important in the pathogenesis of arteriosclerosis. If this is so, oestrogens may, in future, play an important role in the prevention of this type of arterial disease.

The study of salt and water metabolism in response to sex steroids gives further information about their action. Androgens and oestrogens can affect sodium and potassium metabolism. Oedema and salt retention can be induced experimentally. The premenstrual syndrome is probably due to water retention caused by the action of oestrogens in the luteal phase of the cycle (figure 9). The distribution of fluid between intracellular and

extracellular compartments is the result of osmotic action and is mainly dependent on the distribution of sodium and hence the action of mineralocorticoids. Moreover, the renal excretion and reabsorption of sodium, potassium and chloride ions is under the influence of mineralocorticoids and glucocorticoids.

Aldosterone is the steroid hormone with the most powerful salt-retaining action. This action can be damped by peripheral antagonism from progesterone. It seems unlikely that progesterone inhibits the production of aldosterone. Whether or not the aldosterone-progesterone balance has any bearing on the problem of pregnancy oedema is still a matter of debate.

Balance studies have shown that androgens lead to potassium and phosphorus retention. The bony matrix provides evidence to support the concept that androgens not only cause retention of nitrogen but also of minerals. These findings provide the rationale for testosterone treatment in cases of post-climacteric osteoporosis or bony metastases from a primary breast carcinoma.

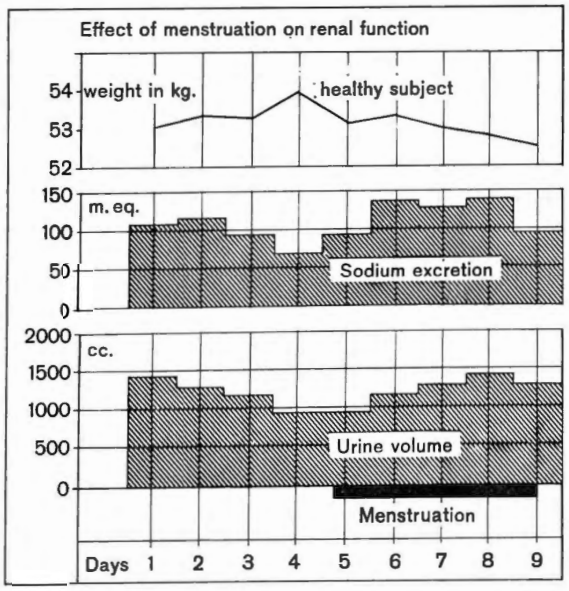



Figure 9. Urine volume, sodium excretion and body weight during menstrual cycle. In the premenstrual phase is a reduction in urine volume and sodium excretion. There is also a clear increase in weight. (*Thorn, G. W., et al.:* Endocrinology **22**, 155 [1938])

A study of tissues dependent on the action of sex hormones has shown that circulatory changes as well as nervous impulses can alter their metabolism *per se*. In vitro studies on certain organs have shown that sex steroids can increase their oxygen consumption and influence their anaerobic and aerobic glycolysis. This action probably depends on the effect of sex steroids on certain enzyme systems.

## III. Action of Hormones on the Female Genital Tract

### a) General Features

The specific action of hormones on certain tissues has already been discussed (page 18). Vaginal epithelium, endometrium and myometrium are all very sensitive to sex steroids which can, in even small amounts, affect their growth and vascularity. Recent work with labelled oestrogens and progestogens suggests a second method of action: it appears that oestrogens accumulate in the uterus as oestradiol, a biologically very active form. In this way even small amounts of sex steroid can have an appreciable effect on the uterus.

The gonads are somewhat exceptional in that their direct response to sex hormones is less than the response which is secondary to the action of sex steroids on the anterior pituitary (page 16).

There is no strict hormonal sex specificity by which androgens act only on the male and oestrogens exclusively on the female genital tract.

**Example:** Although slight differences are detectable, oestrogens as well as androgens call forth proliferative changes in vaginal epithelium. Further, in keeping with what was said in the section on "Classification" (page 1) individual steroids can have more than one sex-specific action.

**Example:** Ethinylnortestosterone has strong progestational and weak androgenic and anabolic actions.

### b) Oestrogens

The effect of oestrogens is best seen in oophorectomised women or in castrated female animals. The genital tract atrophy which follows removal of the ovaries can be prevented by oestrogens. The dosage required for this effect is known as the "proliferative response dose" and, as shown in table I (page 138), is very different for varying compounds. The thickness, vascularity and cellular density of endometrium are all greatly increased by adminis-

tration of oestrogens. Short, round endometrial glands become elongated with long straight ducts. In myometrial tissue, hypertrophy, proliferation and an increased fluid content of individual muscle fibres leads to an increase in the bulk of uterine musculature. Oestrogens also promote the growth and vascularity of the Fallopian tubes. These facts all assume importance in the treatment of genital tract hypoplasia, a subject yet to be discussed. The *vaginal epithelium* undergoes very characteristic changes in response to oestrogens. Oestrogens are responsible for phenomena such as oestrus in rats and karyopyknosis and acidophil staining of cells in vaginal smears. The physico-chemical changes in cervical mucus caused by oestrogens are also very striking. Under the influence of oestrogens alone, a crystallisation or 'fern' pattern appears. A sex specific action of oestrogens is their effect on breast development and early removal of the gonads arrests its many stages.

### c) Progestogens

Secretory change in the endometrium is the most important manifestation of progestogen action on the genital tract. This change depends on the presence of oestrogens. Without preliminary oestrogen-induced proliferative changes, the endometrium is incapable of reacting to progesterone. An increase in phosphatase activity is an early effect. Glycogen storage then occurs in the endometrial glandular epithelium and later in the endometrial stroma. Glycogen can also be recovered from glandular secretions. Further transformations of the endometrium is signalled by appearance of the Golgi apparatus, saw-tooth tortuosity of the endometrial glands and development of the spiral arteries. After an interval of some 14 days, large 'decidual cells' appear in the endometrial stroma.

If, as is normal after an interval of 14 days, the progesterone stimulus is withdrawn, bleeding occurs and all layers of the endometrium, down to the decidua basalis, are shed (figure 10).

The administration of 200 mg. of progesterone over 14 days (see treatment of amenorrhea, page 79, the *Kaufmann test*) can induce the series of physiological changes described above. This dose is known as the "secretory response dose". Other progestogens (e.g. nortestosterone derivatives) do not have the same effect as they have an unduly pronounced action on endometrial stroma without commensurate development of the glands.

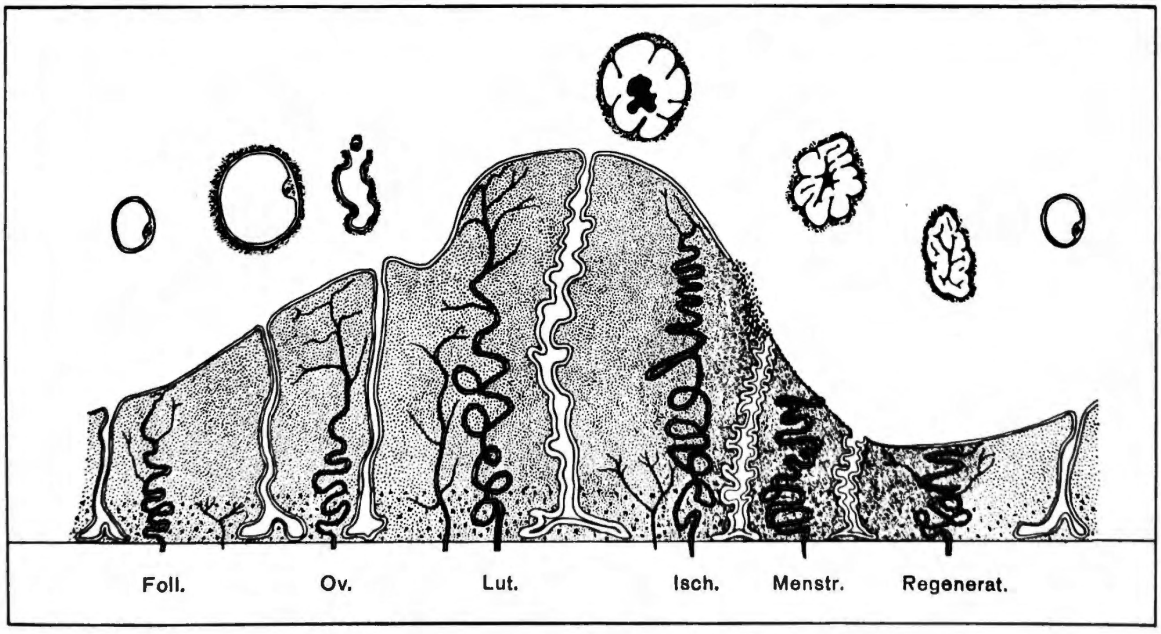



Figure 10. Cyclic changes in the ovary (follicular ripening, ovulation, corpus luteum formation) and the endometrium (its stroma, glands and spiral arteries).

| | | | |
|---|---|---|---|
| Foll. | follicular ripening | Ov. | ovulation |
| Lut. | luteal phase | Isch. | premenstr. Ischaemie |
| Menstr. | menstr. bleeding | Regenerat. | endometrial regeneration. |

(*Bartelmez, G. W.*: Amer. J. Obstetr. Gynec. 74, 954 [1957])

Once a progestogen is administered for more than 14 days, the endometrial glands degenerate, and the previously markedly oedematous stroma begins to shrink. These phenomena are fully discussed in the sections on "Pseudo-pregnancy and Contraceptive Therapy".
With long-term therapy, the smaller the oestrogen content of the progestogens given, the more marked this atrophy is. It extends to pathological lesions such as endometriosis and even, in limited measure, to endometrial carcinoma.
Endometrium which has been rendered proliferative by the action of oestrogens, responds to relatively small doses of progesterone (20—40 mg.) by degeneration and bleeding (page 54—"The Progesterone Test"). In these circumstances, bleeding occurs from the superficial surface of an endometrium which is neither secretory nor pre-menstrual. A sufficiently high dose of progestogens can arrest endometrial haemorrhage without inducing transitional changes (see dysfunctional bleeding, page 88). This benefit is probably the result of direct action on endometrial capillaries.
A progesterone/oestrogen combination is said to dampen muscular activity in the pregnant uterus and cause myometrial hypertrophy in the non-pregnant state. In the presence of progesterone, oxytocin from the posterior pituitary has no action on uterine muscle.
In addition, there is a marked effect on the cervix. Following ovulation, cervical secretions become scanty and the fern pattern disappears.
A luteal effect can be seen in vaginal epithelium. Epithelial cells treated with Papanicolaou stain, become predominantly basophil. Smears show clumping of cells with folding of their edges (page 58).
During pregnancy, progesterone and oestrogens exert a synergistic action on the breasts which prepares them for lactation. Alveolar proliferation and the formation of colostrum are mainly due to luteal hormone.

### d) Androgens

The response of the female genital tract to adrenal and ovarian androgens is less clear cut than is its reaction to oestrogens. It is mainly the development of the clitoris, the labia and pubic hair which are affected by the male sex hormone. Clitoral enlargement and dense pubic hair imply excessive androgen production. The marked effect which even small amounts of androgen have on the developing genital tract of the female foetus (page 26) is worthy of note.
The genital tracts of ovariectomised and hypophysectomised animals show the same response to androgens as to oestrogens. Enlargement of the clitoris and preputial glands, an increase in uterine weight, proliferative changes in the endometrium and vaginal epithelium, have all been produced experimentally by testosterone.
If the adrenals or ovaries produce excessive amounts of androgen or if large doses of testosterone are administered, not only are direct effects seen, but also consequences of the effect of androgens on hypothalamic and anterior pituitary function. Inhibition of ovarian function leads to failure of ovulation. Cyclical, proliferative changes in the endometrium are suppressed and the myometrium atrophies (see treatment of fibroids page 117) or does not develop normally in cases where the influence of androgens begins in the prepubertal stage.
Androgens appear to have a direct action on the breasts as small doses, which have no effect on the menstrual cycle, inhibit the proliferation of breast tissue when directly injected into it.

### e) Synergistic and Antagonistic Actions

The simultaneous influence of different types of steroids may enhance or diminish their individual action on the genital tract (synergistic and antagonistic actions). It is difficult to determine the direct effect of any steroid as it may act not only on genital tract function but also on the hypothalamic/pituitary system. In their physiological proportions of 1:20, oestrogens and progestogens have a synergistic action on the uterus, particulary its endometrium. The secretory effects of progestogens are only seen in the presence of oestrogens. Equally, the genital tract changes seen in pregnancy depend on the simultaneous action of oestrogens and progesterone. If the proportion of progestogens is increased, the two types of hormone antagonise each other. Proliferative changes as well as endometrial gland development regress. Hormonal suppression of ovulation provides a clear example of the antagonistic

action of progestogens (page 105). In spite of added oestrogen, prolonged treatment leads to atrophic changes in the endometrium.
Synergism is also seen in the action of hormones on breast tissue. The small amounts of hormone present in the luteal phase of the cycle are sufficient to occasion slight, cyclical breast enlargement. Increasing amounts of hormone during pregnancy prepare the breasts for lactation. Luteal changes in the cervical mucus and vaginal epithelium (characterised by basophilia and folded cells in a smear) are due to the combined action of oestrogens and progesterone. Pathological changes in the oestrogen/progesterone ratio cause disorders which will be discussed in the clinical section of this book.
The effect of simultaneously administered oestrogens and androgens on the female genital tract depends on dosage levels and the relative amounts of each agent.
In large doses, androgens have an anti-proliferative effect on uterine endometrium. This is an indirect effect of their action on the hypothalamus and anterior pituitary. Although both types of hormone (androgens and oestrogens) can cause proliferative changes in vaginal epithelium, androgens have no karyopyknotic effect. The karyopyknotic changes which occur in response to small doses of oestrogens can be suppressed by androgens. Oestrogens and androgens have an antagonistic action on mammary glands. The former enhance proliferation of breast tissue while the latter have the opposite effect.
The relationship between androgens and progestogens with regard to their action on the female genital tract has only been explored to a limited extent. It has often been observed that androgens have a weak gestagenic effect on endometrium. The possibility of a synergistic action between these hormones therefore exists.

### f) Adreno-cortical Hormones

Under physiological conditions, the influence of adreno-cortical hormones on the female genital tract is negligible. The tissue hypertrophy occasioned by sex hormones is only slightly inhibited by cortisone and related steroids. It can be shown, both in castrated female animals and ovariectomised women, that deoxycorticosterone acetate can have a progestational action. As deoxycorticosterone therapy increases pregnanediol excretion it is possible that DOCA is converted into progesterone. This would explain the progestational effect of DOCA.

### g) Gonadotrophic Hormones

Under physiological conditions, the effects which gonadotrophic hormones (page 7) have on metabolism in general and the genital tract in particular are secondary to their action on the gonads. An exception is the effect of prolactin (luteotrophin) on breast tissue. The latter hormone is essential for the initiation and maintenance of lactation in breasts that have undergone development in response to oestrogens and progestogens. The physiological action of hypophyseal gonadotrophic hormones has mostly been studied in animal experiments. In humans, there is no exact knowledge about the amounts of hypophyseal hormone which are necessary for cyclical ovarian function. It must also be remembered that it is not the action of a single hormone but the quantitative, synchronised interaction of three hormones which is concerned with follicular ripening, ovulation and corpus luteum formation and function.
FSH, which is probably already produced in the luteal phase of the preceding cycle, is responsible for follicular development. Oestrogen is, however, only formed in the follicle when the anterior pituitary starts releasing ICSH (synonymous with LH) as well as FSH. The production of luteotrophic hormone starts at about the time of ovulation and this hormone, together with ICSH, controls the function of the corpus luteum.
In the non-pregnant state, gonadotrophins obtained from the placenta or from pregnant mares' serum, like pituitary gonadotrophins, act only on the gonads. PMS causes follicular ripening. HCG can induce rupture of the Graafian follicle and also prolong the life of the corpus luteum. Its action is independent of anterior pituitary function. FSH augments the action of HCG and hypophysectomy eliminates it.

## IV. Action of Sex Hormones on Target Organs outside the Genital Tract

The many effects which steroid hormones have on peripheral organs are explained by their influence on metabolism (see page 11). These hormones can also exert an action by means of their influence on the autonomic nervous system. Results of experiments sug-

gest that oestrogens mainly provoke parasympathetic activity while progestogens stimulate the sympathetic nervous system. The common observation that illnesses, which are themselves not endocrine in nature, are subject to cyclical variation probably has something to do with the effect of ovarian hormones on the autonomic nervous system.

Further phenomena are now described which demonstrate the manifold action of sex hormones on body functions.

*Skin* and *mucous membranes* are influenced by all sex hormones. They stimulate cellular proliferation and cause an increase in the thickness of the epidermal skin layer. Androgens augment the function of sebaceous glands while oestrogens have the opposite effect. Progestogens make the skin more smooth. The epithelia lining the mouth and the bladder are subject to the same cyclical variations as vaginal epithelium.

The growth of *scalp hair* is said to be promoted by oestrogens, which are even effective as local applications.

The *peripheral circulation* is also increased by oestrogens. This effect is the result of acetyl choline being released by stimulation of the autonomic nervous system.

The growth of *long bones* is furthered by small doses of oestrogens and androgens. Large doses of hormones can lead to early fusion of the epiphyses.

Steroids have a varying effect on *bone marrow* function. In large doses, oestrogens inhibit erythropoiesis while androgens stimulate the production of erythrocytes.

*Liver* and *kidney* are examples of parenchymatous organs on which androgens have a protective action in that they prevent degenerative changes with certain toxic agents. In addition, oestrogens protect renal tubular function but they may, in certain circumstances, occasion fatty changes in the liver.

Oestrogens have often been observed to bring about a fall in serum *lipid* and *cholesterol* levels (arteriosclerosis treated by oestrogens) while androgens have a slight contrary effect.

In relatively small amounts, androgens cause structural changes in the female *larynx* and a deeper voice.

Although it is difficult to present objective evidence thereof, sex hormones undoubtedly have an effect on the *central nervous system.* Testosterone, in particular, stimulates cerebral function. Mental ability (powers of observation and concentration) often increases to the point of euphoria.

There is an undoubted connection between ovarian hormones and female *sex-drive.* This effect was, however, formerly overestimated. Studies on amenorrhoic or oophorectomised women show that a woman's sexual drive, as distinct from that of a man's, is not appreciably altered by gonadal failure. Androgens may cause an undesirable increase of libido in women (see treatment of breast carcinoma).

# F. Physiology of Hormones at Different Stages of Development and Maturity

## I. Prenatal Life

The endocrine system develops in the first months of foetal life. The differentiation of primordial germ tissue into testes or ovaries is determined by the chromosomal constitution of the fertilized egg.

This consists of 22 autosomal pairs and 2 sex chromosomes. Ovaries develop in the presence of 2X chromosomes, while male gonads develop with one X and one Y chromosome. In certain abnormal states which are discussed in the chapters on amenorrhoea and intersexuality, the genital tract develops as in females, regardless of a male sex chromosome constitution.

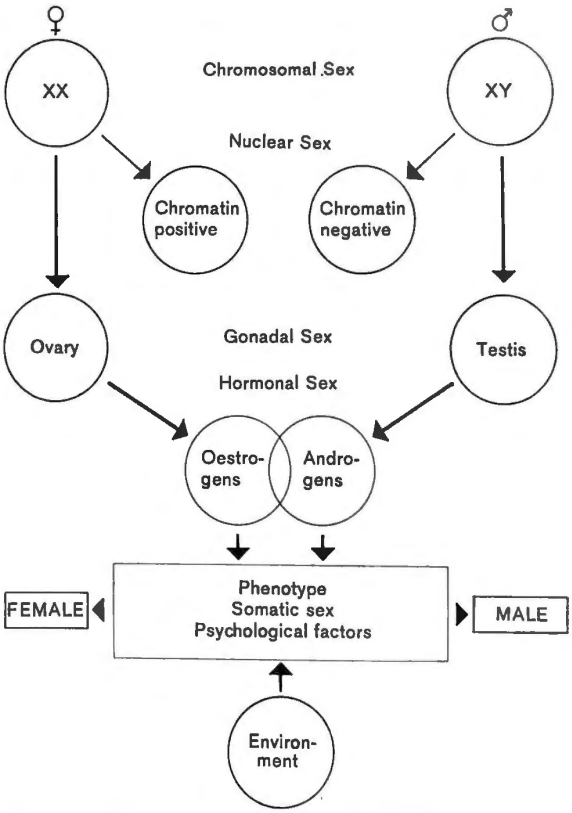



Figure 11. Factors which determine "Sex".
(*Zander, J.:* Mkurse. ärztl. Fortb. **12**, 432 [1962])

Many investigations have been aimed at providing answers to the question of when and to what extent endocrine glands function during foetal life. Such investigations are complicated by the transfer of maternal hormones across the placental barrier.

Observations on anencephalics and the results of animal experimental, intra-uterine decapitation suggest that the hypothalamus and

anterior pituitary do have a certain action on dependent glands. The afore-mentioned interruption of hypothalamic and anterior pituitary function leads to arrest of gonadal and adrenal development. Decapitation of male rabbit foetuses between the 19th and 24th days of gestation results in feminization of the genital tract.

In the last months of intra-uterine life, foetal ovaries appear to be relatively large. They contain numerous primordial follicles. The male gonads, on the other hand, already produce androgens at 3 months' gestation and these hormones provoke masculinization of the genital tract. The foetal adrenals are relatively large during the last trimester of pregnancy. The zona reticularis shows particularly marked hypertrophy. Biochemical analyses of extracts from foetal adreno-cortical tissue show that relatively copious amounts of corticoids, particularly dehydro-epi-androsterone sulphate, are formed from the 7th month of pregnancy onwards. These findings suggest that the foetus can produce adrenal steroids in significant amounts and that these are undoubtedly of some importance to its metabolism (figure 12). It may also be assumed that foetal adrenal hormones are used by the placenta as oestrogen precursors.

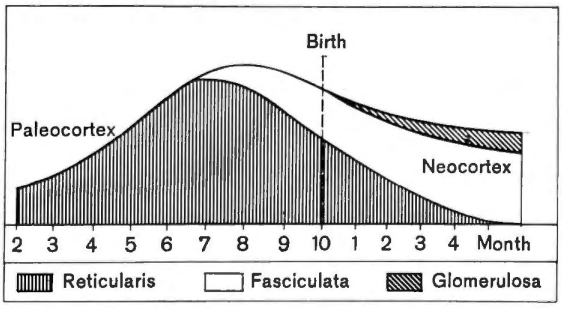



Figure 12. Development of the adrenal before and after birth.
(*Botella-Llusia, J.*: Klinische Fortschritte der Gynäkologie, München 1954)

The foetus is sensitive to the action of maternal hormones that cross the placental barrier. The uterus of the newborn female infant, particularly the cervix, shows signs of oestrogenic stimulation. An infant's breasts may demonstrate similar effects (mastopathia neonatorum). These changes are, however, not commensurate with the high levels of circulating oestrogen in the foetus.

The disparity between hormone levels in pregnancy and the oestrogenic changes seen in certain foetal organs is explained by specific peculiarities of foetal metabolism. These effectively diminish the action of oestrogenic and progestational placental hormones which enter the foetal circulation through the umbilical vein:

### I. Oestrogens

Oestradiol is inactivated by conversion into oestrone or oestriol. In addition, rapid conjugation of steroids dampens their oestrogenic action.

### II. Progestogens

Progesterone is broken down to 20α- and 20β-hydroxy-pregn-$\Delta^4$-en-3-one. The latter probably is converted back into progesterone when it reaches the placenta through the umbilical artery. Thus we have a *uteroplacental-foetal* circulation.

### III. Chorionic Gonadotrophin

Chorionic gonadotrophin, which is formed in large quantities during the first half of pregnancy, has no physiological action on foetal endocrine glands. In certain disorders (pre-eclampsia or diabetes), high urinary levels may be found. Autopsy studies on cases of pre-eclampsia suggest that the foetal ovaries show evidence of excessive stimulation by chorionic gonadotrophin.

The embryo is particularly sensitive to the influence of exogenous hormones at certain stages in its development. During organogenesis (between 15 days' and 12 weeks' gestation), genital tract development in a female foetus may be disturbed by small doses of androgen or by larger doses of progestogen with an androgenic side effect. This results in enlargement of the clitoris and the labia. In marked cases, the labia fuse posteriorly. These complications have also been observed in the newborn female infants of mothers given stilboestrol during pregnancy.

These malformations can be produced in rat foetuses by experiments using the drugs described at various levels of dosage. The association of cause and effect means that the prescription, during pregnancy, of steroids known to have a virilizing action on the foetus, amounts to misguided clinical practice (see pages 48, 112).

## II. Childhood

The hypothalamus and anterior pituitary of a child hardly influence the gonads during the first few years of life. The onset of ovarian

function signals an increased production of gonadotrophic hormones by the anterior pituitary. This, in turn, is the result of maturation of the hypothalamus.

Animal experiments show that the development of the hypothalamic/anterior pituitary system follows a remarkable pattern. It is, for example, possible to influence the onset of sexual maturity in rats and monkeys by administering oestrogens or androgens during just the first 5 days of life. Constant oestrus with failure of cyclical changes develops. Without any doubt, hormone therapy has here caused irreversible damage as a result of its central action. The simultaneous administration of reserpine or progesterone cancels this effect, with normal subsequent reproductive function. It is not known whether these remarkable observations are applicable to humans. They do, however, permit the following conclusions:

I. The hypothalamic/anterior pituitary system of both male and female mammalian foetuses is, basically, tuned to future cyclical function.

II. The effect of foetal testicular androgens on the midbrain destroys this potential.

Until the age of 8 years, gonadal function is insignificant. The general appearance of normal girls hardly differs from subjects of the same age with no germinative tissue (ovarian agenesis). The oestrogens produced by the ovary are insufficient to cause sexual development during childhood. At the age of 8 to 9 years, the body build begins to alter. At the same time, the ovaries enlarge and the production of follicular hormones increases without the occurrence of ovulation or the formation of progesterone. During this stage, the gonads are said to demonstrate "vegetative function". Endocrinologically speaking, childhood ends with this event.

A child's adrenals, having diminished in size and corticosteroid content immediately after birth, play an important role in general development during the early years of life. At the end of this time, the adrenals also show signs of increasing activity. Until 8 or 9 years of age, the amounts of oestrogen, 17-ketosteroids and gonadotrophic hormones in the urine are barely measurable.

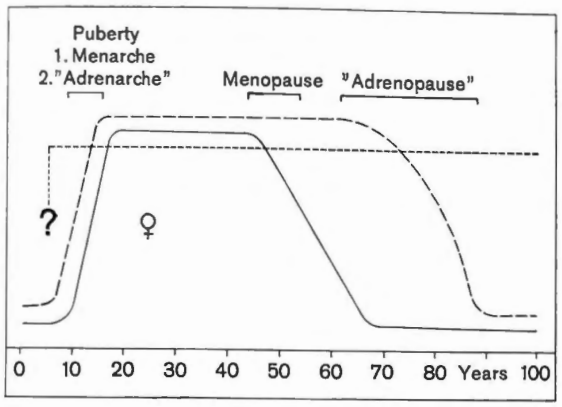



Figure 13. Pattern of hormone excretion during life.
ovarian hormones ———
androgenic adrenal hormones - - -
glucocorticoids .....
(*Albright, F.:* Recent Progr. Hormone Res. 1, 293 [1947])

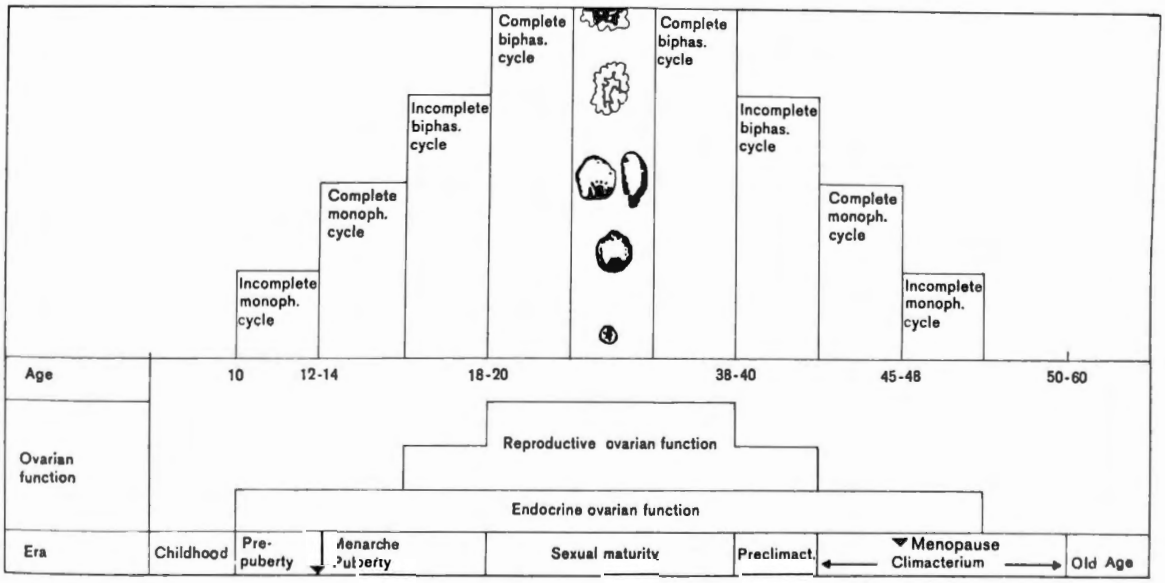



Figure 14. Development and decline of ovarian function according to Tietze.
(*Elert, R.:* Regensburg. Jahrb. ärztl. Fortb. **6,** I [1954/55])

The genital tract, particularly the uterus, hardly enlarges during childhood. Indeed, the weight of the uterus diminishes during the first few years. Rapid development of the genital tract follows the onset of ovarian function.

## III. Puberty

At about the age of 10 (or when childhood ends) puberty begins. It lasts until about 16 years when physical development is virtually complete. The first years of this important period are marked by considerable skeletal growth and the development of secondary sex characteristics. The menarche is a notable event which occurs, not at the end of puberty but half way through it.

Puberty is initiated by the onset of partial ovarian function. Under the influence of gonadotrophic hormones, primordial follicles develop and secrete hormones. To begin with, follicular rupture does not occur and hence neither corpora lutea nor progesterone are formed. Early menstrual periods are often anovulatory although they betoken cyclical function of the hypothalamic/anterior pituitary/ovarian axis.

The increase in size of the adrenal cortex is an important process in the maturing girl. Not only glucocorticoids and mineralocorticoids but also androgens are produced in increasing amounts.

By analogy with the menarche, some describe increasing function of the pubertal adrenal as the "adrenarche" (figure 13).

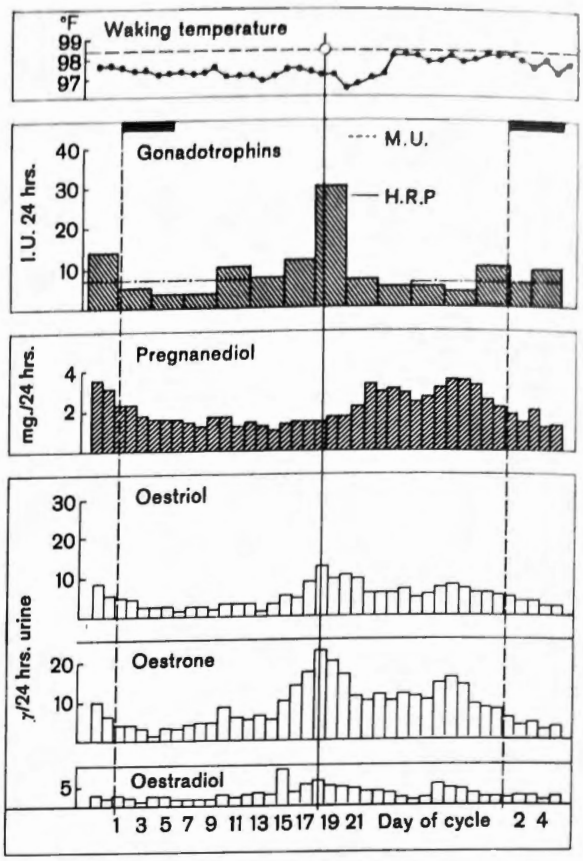



Figure 16. Daily excretion of gonadotrophins (mouse uterus assay = M. U., H. R. P. = ICSH test in the hypophysectomised rat prostatic gland), pregnanediol (estimated by Klopper's method) and oestrogens (measured by Brown's method) in a 27-year old patient. Ovulation (o) occured on the 18 th day recognised by an increase in gonadotrophin and oestrogen excretion. Menstruation commenced on the 33rd day. (*Brown, J. B.*, et al.: J. Endocr. 17, 401 [1958])

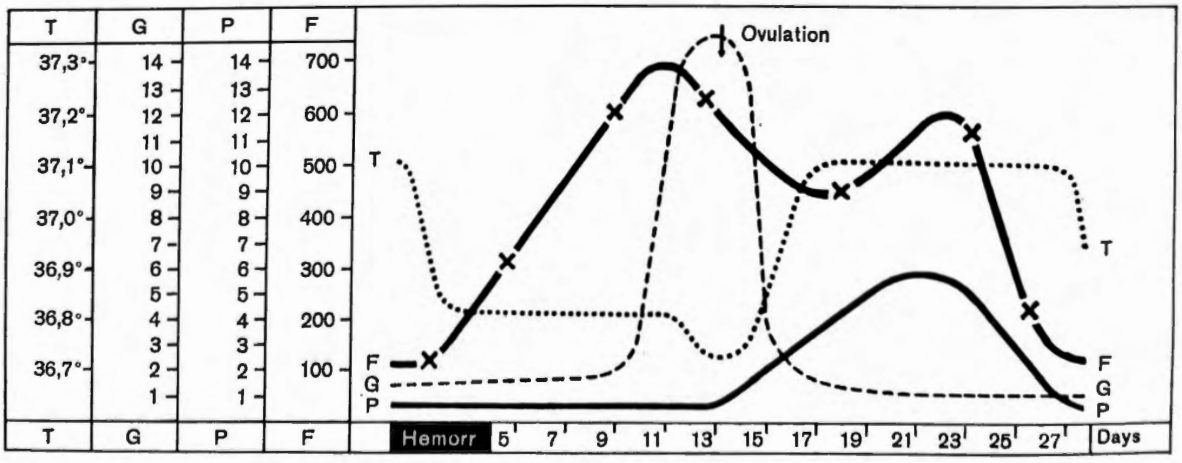



Figure 15. Historical concept of urinary hormone excretion and basal body temperature during a normal menstrual cycle modified by Selye.

T = basal body temperature in °C
G = gonadotrophins in I. U./24 hours
P = pregnanediol in mg/24 hours
F = oestrogens in I. U./24 hours.

(*Selye H.*: Textbook of Endocrinology [1947])

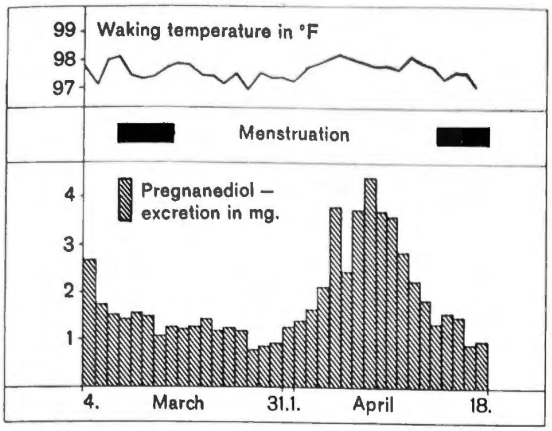



Figure 17. Pregnanediol excretion and basal body temperature during a normal menstrual cycle.
(*Klopper, A. I.:* J. Obstetr. Gynaec. **64**, 504 [1957])

Oestrogens and slowly increasing amounts of adreno-cortical hormones (particularly androgens) determine the appearance of a girl in puberty and influence the development of the breasts and genital tract. Urinary hormone excretion studies show that there is a relationship between maturity and the functional status of endocrine glands.
Subjects who develop slowly or incompletely show lower levels of hormone excretion than more precocious individuals of the same age.

## IV. Sexual Maturity

Reproduction occurs during the years of sexual maturity. These years start with the first biphasic cycle (follicular growth, follicular rupture and corpus luteum formation) and ends with extinction of the "vegetative function" of the ovary. Sexual maturity spans a period of about 30 years. Its duration depends on the number of follicles available in the ovary.
The reproductive and endocrine functions of the ovary and their relation to the hypothalamus and the anterior pituitary form the centre point of cyclical menstrual activity.
Morphological changes in the ovary mirror its reproductive function. The original stock of primordial follicles numbers about 500,000. At 4 weekly intervals, a *Graafian* follicle matures, grows to a diameter of 10 to 15 mm and reaches the surface of the ovary pushing aside other constituent tissues. Between the 10th and 14th days, the follicle ruptures. The ovum, together with follicular fluid, is discharged into the abdominal cavity and enters a tubal ostium.

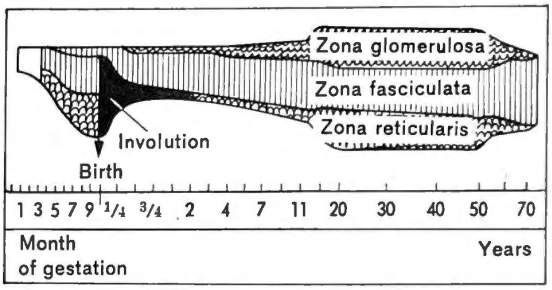



Figure 18. The human adrenal cortex through life.
(*Rotter, W.:* Virchows Arch. **316**, 590 [1949])

With collapse of the wall of the follicle and luteinization of its granulosa cells, it is transformed into a corpus luteum. The life span of the corpus lutuem is 14 days. It then degenerates forming a corpus albicans. Some 350 to 400 follicles are "used up" in this way.

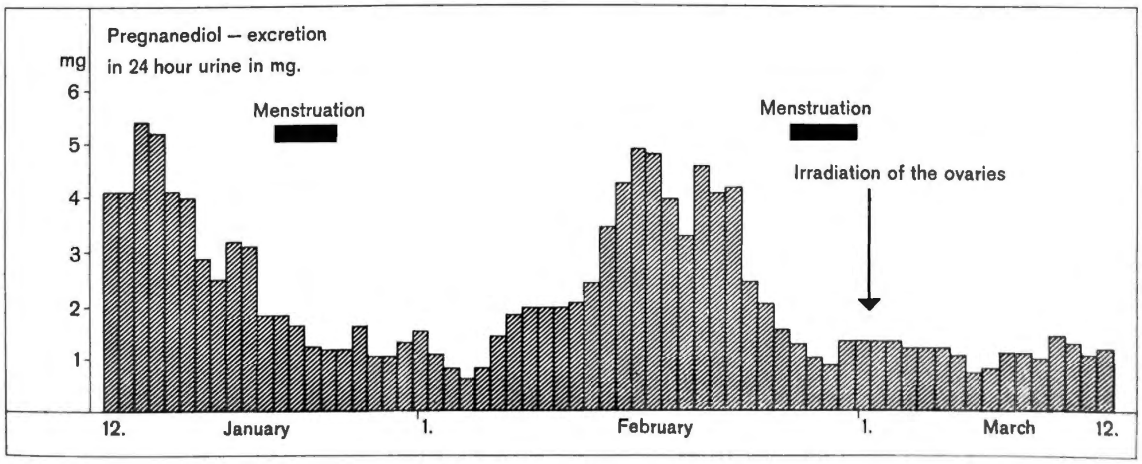



Figure 19. Effect of X-ray castration on pregnanediol excretion.
(*Klopper, A. I.:* J. Obstetr. Gynaec. **64**, 504 [1957])

The endocrine function of the ovary is closely linked with reproduction as it consists of releasing oestrogens, progesterone and androgens into the blood stream with the overriding purpose of preparing the uterus for nidation of the fertilized egg.

Oestrogens from the *Graafian* follicle, as well as androgens, are probably formed before, after and during the years of sexual maturity. *Per contra*, the ovary can only secrete progesterone in association with ovulation. The range of hormone production is subject to cyclical variation (see figures 16 and 17).

It is reasonable to assume that the quantity of oestrogens produced by the ovary greatly exceeds the amounts of oestriol, oestrone, oestradiol and other oestrogen metabolites recovered from the urine (see page 12). During a menstrual cycle, the total estimated output is 10 to 20 mg. with highest levels at the time of ovulation and in the pre-menstrual phase (see figure 16).

The sites of oestrogen production are, first and foremost, the ripening follicle and the granulosa cells of the corpus luteum.

Oestradiol and oestrone, but not oestriol, can be recovered from these sites.

The production of progesterone which begins shortly before ovulation and ends just prior to the onset of menstruation, can be estimated by measuring the pregnanediol excretion during this time interval. This is in the range of 200 mg. per menstrual cycle (see figure 17).

The levels of androgen production, as well as the question of their cyclical excretion are not settled with certainty. Their significance cannot be too great, for suppression of adrenal function with dexamethasone leads to the almost complete disappearance of 17-ketosteroids (androgen metabolites) from urine. Of the compounds normally found in urine, androsterone and aetiocholanolone are thought to be of ovarian origin. Dehydro-epi-androsterone and the 11-oxo and 11-oxy derivatives, aetiocholanolone and androsterone, stem from the adrenal. The total amount of androgen produced by the sexually mature woman is about twice the daily 17-ketosteroid excretion of 10 to 15 mg.

The adrenals (figure 18) do not show cyclical activity as they are under the control of ACTH rather than of gonadotrophins. Androgens as well as gluco- and mineralo-corticoids are produced continuously. It is also worth noting that the amount of progesterone produced by the adrenals is constant and not subject to cyclical variations. This accounts for 1 mg. of pregnanediol in a 24-hour specimen of urine (see figure 19). The small amounts of oestrogen produced by the adrenal of a sexually mature woman are relatively insignificant.

The cyclical excretion of sex hormones leads to a series of synchronized events in the genital tract. During the time of follicular ripening, the endometrium undergoes proliferative changes in response to oestrogens. After follicular rupture, and under the simultaneous influences of progesterone and oestrogens, secretory changes appear in the uterine endometrium (see page 21). These could also be called the changes of the "pre-gravid phase" as they are preparatory to possible nidation. The morphological changes in the endometrium are associated with numerous biochemical events. The most notable of these is an increase of alkaline phosphatase activity at the time of ovulation and the formation of glycogen in endometrial stroma and glands during the luteal phase of the cycle.

If the ovum is not fertilized, the function of the corpus luteum fails after an interval of 14 days and is associated with degeneration of the uterine endometrium. This starts with pre-menstrual shrinking of endometrial tissue. Bleeding then occurs from the spiral arteries exposed by shedding of functional layers of the endometrium. After several days, the basal epithelium regenerates and proliferative changes in the endometrium appear anew as a result of oestrogen from the next ripening follicle.

The associated changes in the vaginal epithelium can be described in 5 phases:

1. Menstrual phase (day 1 to day 4): The vaginal smear contains mainly basophil cells as well as numerous leucocytes.

2. Post-menstrual phase (day 5 to day 8): The smear shows mainly basophil cells with fewer leucocytes.

3. Oestrus phase (day 9 to day 14): Under the influence of increasing amounts of follicular hormone, more acidophil cells appear. Hardly any leucocytes are now visible.

4. Post-ovulatory phase (day 15 to day 18): The number of acidophil cells is unchanged but they tend to appear in clumps. Basophil cells and leucocytes again become visible.

5. Pre-menstrual phase (day 19 to day 28): The number of basophil cells increases. There is clumping of cells and evidence of desquamation.

There is also a relation between cervical secretion and the phase of the menstrual cycle. Just after menstrual bleeding, the cervical canal appears to be closed. Cervical secretion is not very copious. Just before ovulation, copious amounts of thin cervical secretion are seen. Its "Spinnbarkeit" or "threadability" is particularly noticeable at this time. A few days after ovulation, the amount of cervical mucus again decreases as does its "Spinnbarkeit". Alterations in the mucus may also be seen in a dried smear. Between the 7th and 20th days of the menstrual cycle, a "fern pattern" is seen as a result of crystal formation. If ovulation has occurred, the "fern pattern" is not seen from the 20th to 26th days of the cycle. The fact that these physico-chemical changes do not occur without ovulation is of clinical diagnostic importance (see page 102).

It is generally accepted that the specific biochemical characteristics of alkaline cervical mucus at the time of ovulation facilitate sperm migration into the upper genital tract. By contrast, sperm penetrability is reduced or absent during the luteal phase of the menstrual cycle. Waking temperature records are of great diagnostic importance.

About one to three days after ovulation, the temperature rises by about 0.5° C. as a result of the central thermogenic effect of progesterone. This rise in temperature is maintained until the onset of menstruation.

Breast development commences before the menarche. This occurs in several stages and is the result of increasing amounts of oestrogen. Full female breast maturation appears only when the breast alveoli develop in response to progesterone. Oestrogens and progesterone thus act synergistically.

## V. Pregnancy

Early pregnancy is characterised by increased hormone production by the corpus luteum of pregnancy. Soon the placenta becomes the main site of hormone production. The growth and well-being of the pregnancy depend on the rising amounts of hormone which later reach considerable proportions. Nourishment and development of the embryo, growth of the uterus, ante-partum changes in the birth canal and in the breasts are all processes which are initiated by ovarian hormones and later maintained by placental hormones (see figure 20).

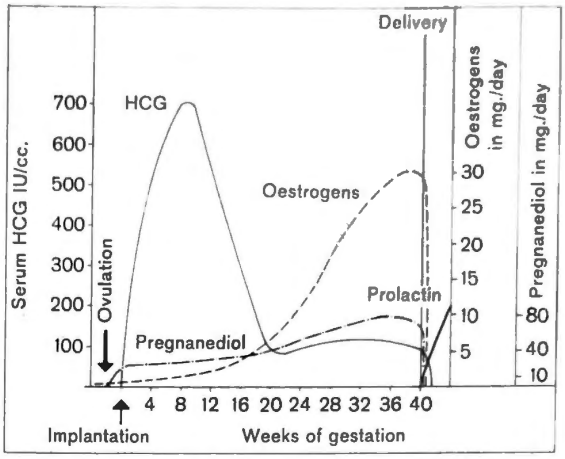



Figure 20. Excretion of chorionic gonadotrophin, total oestrogens, pregnanediol and prolactin during pregnancy and in the early puerperium.

(*Riley, G. M.:* Gynecologic Endocrinology, Hoeber-Harper, New York 1959)

After implantation of the fertilized egg (a process that occurs around the 20th day of the cycle), the body's first protective measure is the inhibition of menstrual bleeding. It is to this end that the ordinary corpus luteum is converted into a corpus luteum of pregnancy. This change is facilitated by the release of chorionic gonadotrophin from the conceptus, even before its implantation in the endometrium. The corpus luteum can thus exceed its normal lifespan of 14 days and continue to produce oestrogens and progesterone in adequate amounts. In this way, endometrial degeneration is avoided. Under the influence of both the sex steroids mentioned, decidual changes occur in the endometrium. The large amounts of circulating oestrogen and progestogen suppress the function of the anterior pituitary and hypothalamus. In this way the development of further follicles remains in abeyance.

The corpus luteum of pregnancy only supports very early gestation. Larger amounts of sex hormone than the corpus luteum can provide are required for nourishment of the embryo and for quiescence of uterine musculature. The young placenta therefore takes over ovarian endocrine function at an early stage, and the corpus luteum then degenerates. Evidence derived from oophor-

ectomy in pregnancy suggests that a pregnancy achieves hormonal autonomy by the second or third month.

The amounts of hormone formed in pregnancy are considerable.

Already during the first days, young trophoblastic tissue produces chorionic gonadotrophin. Between the 19th and 24th days of the cycle, only a few days after ovulation, 100 IU of HCG per 24 hours can be detected in suitably concentrated urine. This measurement is no indication of the effective amounts of hormone which the minute conceptus can produce at this time. It is probable that the amounts produced imply a biosynthetic achievement which has no equal in nature. The HCG levels rapidly rise and, at 40,000 to 200,000 IU per day, reach their peak in the 2nd or 3rd month of pregnancy. From the 4th month onwards, HCG excretion levels fall to values of 5000 to 10,000 IU daily. Later on, a gradual rise is again seen.

The formation of sex steroids steadily increases after the start of pregnancy.

Studies of urinary pregnanediol excretion and progesterone determinations on cord blood show that the daily turn-over of luteal hormone is 100 mg. at first and 200 mg. at a later stage.

The early rise of oestrogen production is gradual, as judged by urinary oestriol and oestrone excretion studies. In the last months of pregnancy, however, appreciable values are attained. As much as 40 mg. of oestrogen can be recovered from a 24 hour urine! The actual production of oestrogens is probably many times in excess of this value as evidenced by recovery studies after injecting hormones (see figure 21).

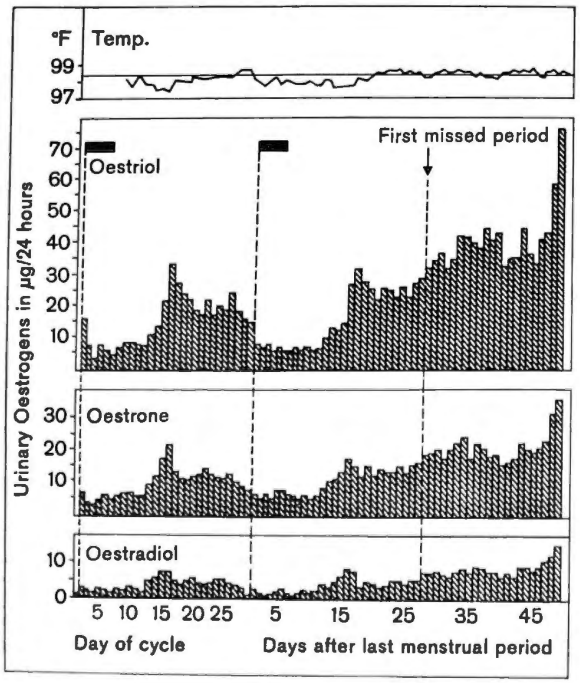



Figure 21. Oestrogen excretion in a 28-year-old woman before and during early pregnancy.
(*Brown, J.-B.*: Lancet **6925**, 704 [1956])

Pregnanediol and oestrogens are found in the copious amounts described until the placenta is delivered. There is no good evidence for the view that steroid hormone levels and the onset of labour are correlated. Considerable amounts of growth hormone are found in maternal and foetal blood. Its presence is necessary for the rapid growth of the embryo.

In addition to oestrogens and progesterone, androgens, ACTH and corticosteroids have been found in placental tissue. It has not been shown whether the latter three hormones are also produced there.

There is conflicting evidence about the behaviour of the anterior pituitary and hypothalamus during pregnancy:

1. Biological assays have shown that anterior pituitary tissue contains only small amounts of gonadotrophic hormone during pregnancy.

2. Enlargement of the pituitary during pregnancy, due mainly to an increase in the number of stem cells, favours increased glandular activity (an increased production of ACTH?).

3. Pregnancy urine contains gonadotrophins of chorionic and hypophyseal origin.

4. In animal experiments, HCG is only effective in the presence of hypophyseal hormones. With the occurrence of pregnancy, ovulation is nearly always suppressed.

These findings suggest that the cyclical function of the hypothalamus and anterior pituitary lapses during pregnancy. It is probable, however, that gonadotrophic hormones are still produced with only small amounts of FSH in the first instance.

Pregnancy is a time of physiological stress and increased demands on the mother. It is not surprising that the adrenal participates in the resulting process of adaptation. The whole gland, and in particular its zona

fasciculata, enlarge. Measurements of corticosteroid metabolites in urine are difficult to assess:

The excretion of aldosterone shows an approximately ten-fold increase. In addition, 17-ketosteroids and 17-hydroxycorticoids are excreted in increasing amounts while the values for 17-ketogenic steroids remain unchanged.

These divergent findings do not necessarily imply increased adrenal function. It is perhaps more likely that it is only the pattern of corticosteroid metabolism which alters during pregnancy in a manner which has not yet been elucidated.

The most striking alteration in pregnancy is the extraordinary increase in uterine size.

In the course of 9 months the weight increases twentyfold, rising from 50 to 1000 g. The size and number of muscle fibres increase. Oestrogens are mainly responsible for the growth of the uterus which is further enhanced by the increase in the size of its contents. Progesterone is responsible for uterine relaxation. A further substance of importance in this respect is oxytocinase which inactivates oxytocin. It is also probable that corticosteroids are concerned in the enlargement of the uterus as a result of their influence on metabolism. Information about the manner in which hormones influence uterine musculature is scanty. It is probable that their effect on water, electrolyte and protein metabolism is important.

The behaviour of vaginal epithelium is a matter of diagnostic importance during pregnancy. Under the influence of oestrogens and progesterone, the smear shows a pre-menstrual pattern. However, the basophil epithelial cells are somewhat smaller, have a vacuolated nucleus and crescentic cytoplasm. Large doses of oestrogen which cause proliferative epithelial changes in the non-pregnant state do not influence the vaginal smear pattern during pregnancy.

The behaviour of the cervical mucus is similar. In a dried preparation, as in the pre-menstrual phase, no "fern pattern" is seen during normal pregnancy. Again, the picture cannot be altered by administration of oestrogens.

Enlargement of the pelvic cavity and widening of the symphysis pubis are changes typical of pregnancy. They may be produced experimentally by sex hormones. Relaxin, a high molecular weight, water-soluble polypeptide, is said to have a particularly marked effect on ligamentous tissue. It is thought that relaxin is formed by the corpus luteum of pregnancy.

Early morning temperature records are of particular interest during pregnancy. After conception, basal temperature stays at the levels normally seen in the luteal phase of the menstrual cycle. In the 3rd or 4th month of pregnancy this level gradually falls by about 0.5° C. It is at this time that the temperature regulating centre becomes resistant to progesterone. After the third month of pregnancy, only very large doses of progestogen can bring about a rise of temperature.

Further pregnancy changes:

*Proliferative activity in the breasts.* This is probably the result of increasing sex hormone levels. *Slight thyroid hypertrophy* is often regarded as a sign of the increasing demands made by pregnancy. The blood volume increases by about one litre. Red cell production more or less keeps pace with this increase so that their number per cubic mm. is about the same. The following metabolic changes of pregnancy should be noted: a positive nitrogen balance, water retention, the retention of minerals, in particular, salt. Pigmentation of the skin is a function of the high concentration of circulating oestrogens. Striae, as with cases of Cushing's syndrome, may represent a change in adrenal function during pregnancy.

## VI. Delivery and Lactation

The onset of labour is characterised by a sudden increase of uterine sensitivity to oxytocin (a posterior pituitary hormone). The other factors involved in bringing about the onset of labour are unknown. When the placenta is delivered, the source of steroid hormones characteristic of pregnancy, together with the source of chorionic gonadotrophin, is lost.

As a result, oestrogen and pregnanediol excretion falls to barely detectable levels within a matter of days. A transient rise in oestriol shortly after delivery is probably due to strong contraction of the uterus which forces blood rich in oestriol into the systemic circulation.

As the ovaries do not immediately resume their hormonal function the puerperium is a time of relative sex steroid deficiency.

The anterior pituitary mainly produces prolactin after delivery. Its direct effect on breast tissue has been established. During pregnancy, when prolactin can be found in small amounts, this hormone together with oestrogens and progesterone seems to support breast development as well as changes associated with

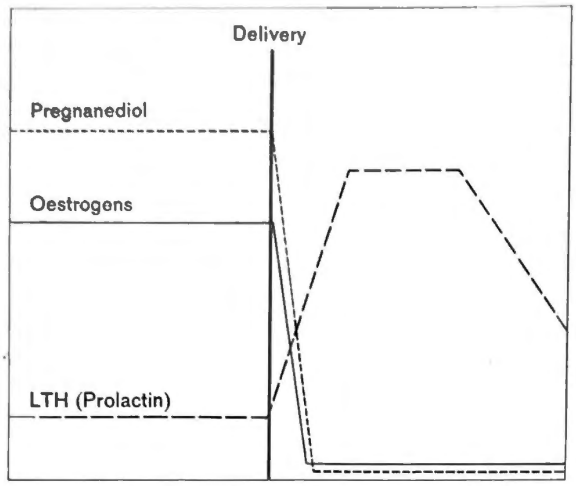



Figure 22. Endocrine status before and after delivery.

preparation for lactation. With the disappearance of steroid hormones, prolactin initiates milk secretion. The sucking reflex is an important factor in maintaining galactopoiesis. It is thought that resulting sensory impulses cause the liberation of oxytocin from the posterior pituitary and prolactin from the anterior pituitary. These hormones are thus of importance in supporting lactation (see figures 20 and 22).

The maternal adrenal reacts to birth, as to any stress, by a transient increase in the output of its hormones. During the puerperium, the adrenal hypertrophy of pregnancy regresses and the output of corticosteroids falls to normal levels.

The first menstrual cycle after delivery signifies the revival of interdependence between ovaries and the hypothalamic/anterior pituitary system.

It usually occurs at the end of the puerperium. As with the first cycles after the menarche, the first episode of bleeding after the puerperium is of the oestrogen withdrawal, non-ovulatory type. Figure 23 shows two small bleedings before the resumption of normal ovulation.

## VII. Climacterium

The climacterium begins with the failure of ovulation and ends with the body's adaptation to a state in which the ovaries are almost entirely without function. When the supply of follicles in the ovary is exhausted, its function ultimately declines. This event usually occurs in the latter half of the fourth decade. Women with an early menarche tend to have a late climacteric. The duration of the climacterium is very variable. It may last anything from several weeks to ten or twenty years.

The climacteric may be divided into several stages, depending on the status of the ovaries.

1. Reproductive function of the ovaries comes to a halt. The supply of potential follicles

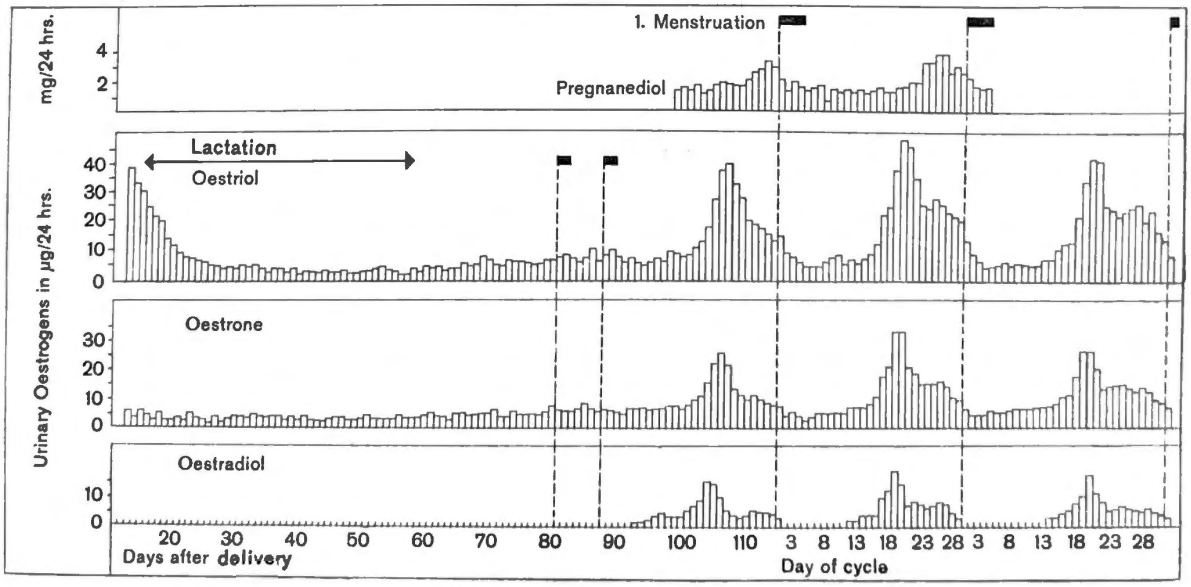



Figure 23. Oestrogen excretion in a 28-year-old woman during lactation and the first two menstrual cycles after delivery.
(*Brown, J. B.*: Lancet **6925**, 704 [1956])

fails, and regular ovulation and corpus luteum formation no longer occur. Follicular hormone is still produced in varying amounts and thus the ovary's endocrine function persists. Endometrial bleeding is now of the oestrogen withdrawal type and is not associated with cyclical secretory changes. This state of continuous "oestrogenization" resembles the condition which prevails in puberty just after the menarche when regular follicular ripening also does not occur. The state of "continuous oestrogenization" is generally considered to be pre-climacteric.

2. Except for a very small resting secretion, the ovaries produce no oestrogens. The resting secretion is insufficient to stimulate the endometrium and as a result menstruation ceases (the menopause).

3. The hypothalamus and anterior pituitary rapidly respond to diminishing levels of sex hormone—"the hyper-gonadotrophic phase". The hypothalamus provokes the release of more FSH and ICSH. The suspicion that "menopausal gonadotrophins" are different in character to those found earlier has not yet been confirmed. Quite often, the output of thyrotrophic hormone also increases.

4. The climacterium is concluded with the appearance of new hormonal balance ("the quiescent state"). The adaptation of the body, with particular regard to the autonomic nervous system and psychological adjustment to growing older, is complete.

In considering these often ill-defined phases of the climacterium, it is obvious that they basically represent graded changes in ovarian function. The store of potentially normal ovarian follicles is exhausted in the fourth decade. Some follicles start ripening and produce hormones but their development is arrested before rupture. Their response to anterior pituitary hormone is obviously diminished. As a sequel, corpora lutea are only rarely found at the time of the climacteric. Soon, follicles entirely disappear from the ovary. The excretion of oestrogens by the ovary is reduced to very low levels which can be measured until a very late age.

It follows that gonadal failure has repercussions in the *whole endocrine system*. The hypothalamic/anterior pituitary axis is adjusted to a well-defined cyclical variation of hormone levels. The reduction of oestrogen and cessation of progesterone secretions lead to anatomical and functional changes in the anterior pituitary. Its weight increases and, as with castrates, a certain type of cells appears which betokens an increased production of gonadotrophins.

It has often been said that the adrenal produces more sex steroids after the menopause. Investigations have, however, led to quite the opposite conclusion and the increasing amounts of circulating gonadotrophin seem to provoke no increase in adrenal function. Neither the corticoid nor the 17-ketosteroid excretion which is attributable to adrenal function is much influenced by ovarian failure.

The thyroid gland, dependent as it is on its trophic hormone and on the autonomic nervous system, is often affected by the climacterium. It shows a tendency towards hyperfunction which is probably more often due to disturbances in the autonomic nervous system than to excessive stimulation by the anterior pituitary.

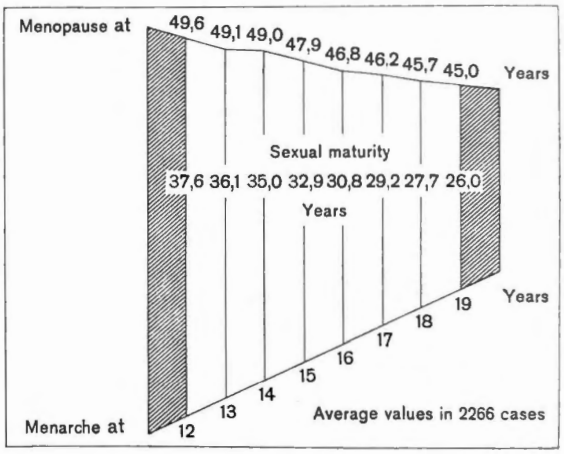



Figure 24. Relationship between ages at the menarche and menopause.
(*Goecke, H.:* Arch. Gynäk. **193**, 33 [1959])

Dysfunction of the hypothalamus not only affects the anterior pituitary and peripheral endocrine glands but also general metabolic processes. An excessive intake of fat or other foods may follow an autonomic disturbance. In such circumstances, factors such as individual constitution or the type and amount of food consumed may be of considerable significance.

The phase of excessive gonadotrophic activity is characterised by many autonomic and psychological disturbances which appear to be a transient accompaniment of at least 60 per cent of climacteria. This high percent-

age indicates how very difficult is the adaptation of a woman's physiology and psychology to these circumstances. Hot flushes, hot sweats, insomnia and depression are most often noticed. The assumption that the severity of symptoms depends on the amount of gonadotrophin being produced must be doubted. It is probable that constitutional factors are of importance. Women who show disturbances of an autonomic nature during their years of sexual maturity are more easily affected by climacteric symptoms. Tests of hypothalamic function (Staub-Traugott, adrenal sensitivity and water-loading tests) tend to be abnormal in subjects demonstrating severe hormone withdrawal symptoms at the time of the climacterium.

Physiological ageing of the ovary has varying effects on peripheral organs. It is most marked in those tissues most strongly influenced by sex steroids.

Uterine endometrium is most affected. In the follicular phase of a cycle, proliferative changes may be excessive giving cystic glandular hyperplasia without secretory changes in the latter phase of the cycle. After the menopause, the endometrium still shows proliferative activity for considerable periods of time and it remains sensitive to the action of hormones. Suitable doses of oestrogen, progesterone or androgen can mimic all the stages of endometrial activity normally seen in sexually mature women.

The vaginal epithelium mirrors the hormonal status of the climacterium. Before the menopause, variable amounts of proliferative activity may be seen which do not always tie up with the endometrial status. After the menopause, the presence of moderate proliferative activity allows one to draw certain conclusions: it must be the result of small amounts of oestrogen and reflects the androgenic action of adrenal steroids.

## VIII. Post-Climacterium and Old Age

With the cessation of menopausal symptoms, the post-climacteric era begins. Its duration is as variable as the duration of the climacterium. It is characterised by adaptation of the hypothalamus and the autonomic nervous system to the situation created by gonadal failure. This process of adaptation is not seen in other endocrine glands. The anterior pituitary continues to secrete gonadotrophins in large amounts (figures 25 and 26).

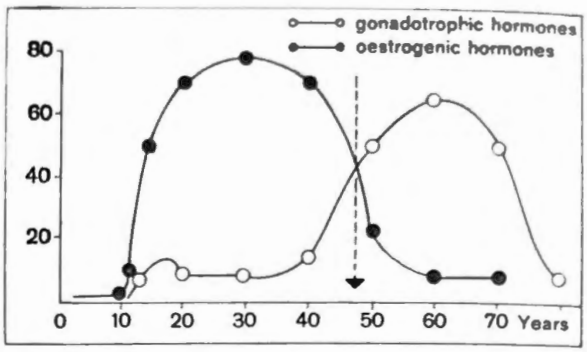



Figure 25. The excretion of oestrogenic and gonadotrophic hormones in puberty, sexual maturity and old age.
(*Pedersen-Bjergaard* a. *Tonnesen:* Acta endocr. 1, 38 [1948])

The formation of steroid hormones in women, as judged by the excretion of various urinary metabolites, is characterised by evidence of

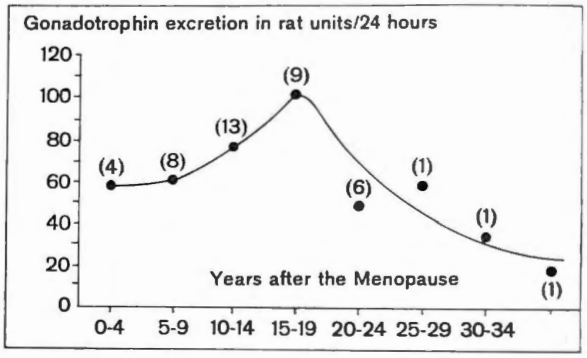



Figure 26. Urinary gonadotrophin excretion in postmenopausal women at 5-year intervals.
(*Albert, A.:* In *Engle, E. T.* & *Pinkus, G.*, Hormones and the ageing Process 56 [1956])

considerably reduced oestrogen production in later years. As a result the excretion pattern resembles that normally seen in men (figures 27 and 28).

Ultimately, the post-climacteric phase gives way to old age in which the most characteristic process is atrophy of many organs and tissues.

The tendency to atrophy is very variable. It is most marked in those organs whose function and metabolism depends on the presence of sex hormones. The genital apparatus, breasts and bone matrix are particularly affected. Skeletal osteoporosis appears. It is probably the direct result of inadequate amounts of sex hormone characterising old age.

Where the endocrine glands are concerned, atrophy is most marked in the ovaries, their weight decreasing by 50 per cent.

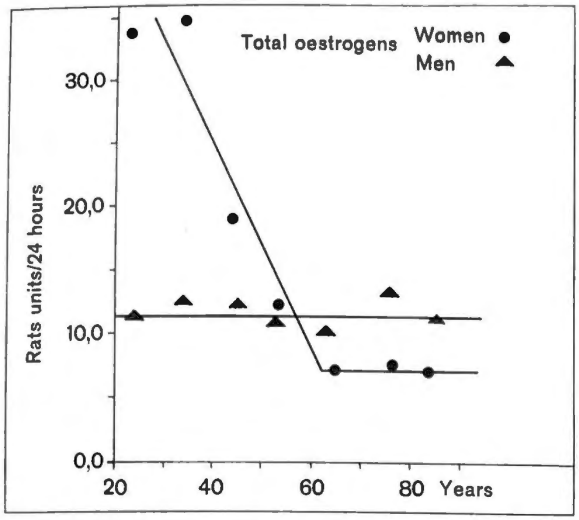



Figure 27. Total oestrogen excretion in males and females expressed in rat units/24 hours.
(*Pincus G.:* In *Engle, E. T.* & *Pincus, G.*, Hormones and the ageing Process, 6 [1956])

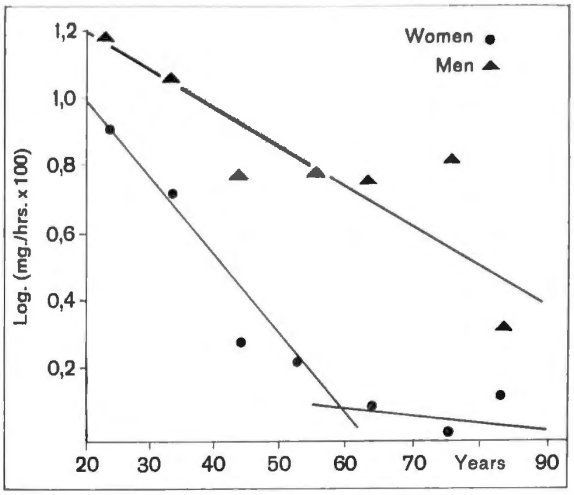



Figure 28. Androgen activity in 24-hour urines from both sexes.
(*Pincus G.:* In *Engle, E. T.* & *Pincus, G.*, Hormones and the ageing Process, 6 [1956])

The adrenals, thyroid and anterior pituitary do not reflect the ageing process so distinctly. It is true that their weight decreases but they do not undergo senile atrophy.

The uterus, vagina and breasts, all of which are dependent on oestrogens, show the most marked tendency to atrophy. This often occurs shortly after the menopause and before any changes are noticeable in other organs. In advanced age, widespread body changes are seen due to alterations in metabolism and cellular function. All anabolic processes slow down, while all catabolic activity continues at the same rate. In other tissues, an increase in dry weight can be noted due to increased storage and density of tissue colloids. This leads to a diminution in functional capacity.

Virilization, often occurring alongside the atrophy of old age, is a process which should be mentioned. The similarity between metabolic processes of men and women at this age (as judged by mainly androgenic sex hormone excretion) is undoubtedly responsible for the masculinization often seen in advancing years. It is naturally most marked in those women who already had a male hair distribution during the years of sexual maturity.

# G. Therapeutic Use of Hormones

## I. General Principles

Endocrine disorders are mostly the effect of disturbances in the control or regulation of one or more endocrine glands. These disorders are as frequently due to hormone deficiency as to hormone excess. Occasionally, an alteration in hormone balance is seen when the deficient production of one hormone is associated with increased production of another. Not infrequently, disturbances in one endocrine gland affect the function of others. The hypothalamus and anterior pituitary are frequently important points in the pathway of such a mechanism (see page 16). A distinction must be made between disturbances due to primary dysfunction of peripheral endocrine glands and those of central origin. Hormonal balance can also be disturbed by failure of the liver, an organ involved in their breakdown and metabolism.

Endocrine disease may also be mimicked by interference with the action of hormones at the end-organ receptors. For example, menstruation does not occur, even in the presence of normal ovulation, in circumstances where the endometrium is so poorly developed that it is incapable of function.

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**Example of a disturbance due to hormone deficiency:** Secondary amenorrhoea due to diminished gonadotrophin output.

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**Example of a disturbance due to hormonal excess:** Post-menopausal bleeding due to an oestrogen producing ovarian tumour.

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**Example of a disturbance due to hormonal imbalance:** Excessive gonadotrophin production due to hormonal deficiency of the ovary in cases of dysgenesis or agenesis of the gonads.

---

**Example of interference with the action of one endocrine gland due to a disorder in another:** Secondary ovarian failure and amenorrhoea in cases of adreno-genital syndrome.

---

**Example of a disturbance due to disorder of end-organ receptors:** "Silent cycles" (see page 83) due to a failure of endometrial response in the presence of normal ovarian function.

---

Although hormone therapy can affect these disorders in a number of ways, it often cannot

take all aspects into consideration. The dose of hormone administered, the timing and the duration of hormonal effect are often of critical importance in this respect.

Every treatment with hormones not only has peripheral effects but also acts on the hypothalamic/anterior pituitary system. The effect of long-term low dosage steroid therapy is mainly on peripheral organs. Large doses of sex hormone influence the hypothalamus and anterior pituitary even after a short time. Gonadotrophins cannot act without pre-existent gonadal function. The central and peripheral effects of treatment with hormones are of limited duration. Withdrawal of hormones often leads to recurrence of a particular disorder. Frequently, however, a permanent cure is achieved provided that the original dysfunction is not based on a fundamental error in regulating mechanisms.

The following are possible methods of treatment:

### a) Substitution Therapy

Disorders due to hormone deficiency caused by failure of an endocrine gland can be treated by administering the specific hormone concerned or a substance which has a similar action. In cases where the affected gland is irreversibly damaged substitution therapy must be life-long. Long-term treatment with physiological doses of sex hormones, for example, normalizes the anterior pituitary output of gonadotrophic hormones.

**Example:** Substitution therapy with sex hormones in cases of ovarian dysgenesis or agenesis or in castrated subjects.

### b) Stimulation Therapy

Endocrine failure due to deficient stimulation by the anterior pituitary can be treated with the appropriate trophic hormone which stimulates the otherwise normal endocrine gland.

**Example:** Gonadotrophin treatment of amenorrhoea due to pituitary or other central deficiencies.

### c) Suppression Therapy

Short or long term administration of steroid hormones in high doses effectively suppresses the function of corresponding endocrine glands. The effect of the administered hormones on the anterior pituitary and hypothalamus is important in producing this result. The identity of the trophic hormone affected depends on the nature of the hormone administered. Thus oestrogens inhibit FSH production and cortisone prevents the formation of ACTH. The inhibition is of limited

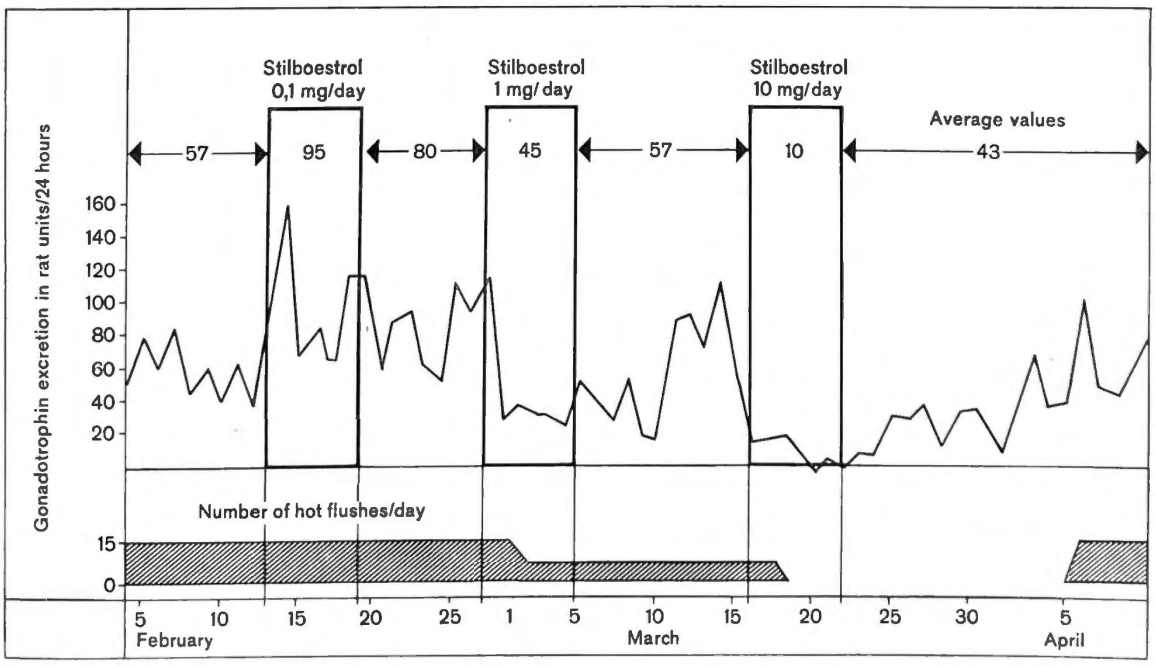



Figure 29. The effect of stilboestrol on the urinary gonadotrophin excretion in a castrated woman. (*Albert, A.*: Recent Progr. Hormone Res. 12,227 [1956])

duration. After discontinuing treatment, the anterior pituitary quickly recovers, indeed it may even show a rebound effect (fig. 29).

This enhancement of anterior pituitary function means that at the end of treatment with hormones, previously defective endocrine glands begin to function normally.

**An example of short-term suppression therapy:** Daily injections of 10 mg. of oestradiol benzoate from the fourth to the sixth days of a cycle can delay ovulation by several days (see treatment of polymenorrhoea, page 93).

**An example of cyclical suppression therapy:** The administration of an oestrogen-progestogen combination (Anovlar) from the fifth to the twentyfifth days of a cycle leads to suppression of ovulation.

**An example of long-term suppression therapy:** High doses of oestrogen and progestogen administered for, say, eight weeks lead to complete suppression of ovulation and menstruation. A previously disturbed cycle may become normal after treatment. This demonstrates the rebound phenomenon (see pseudo-pregnancy, page 97).

### d) Local Treatment

Growth and proliferation of an organ may be produced by local use of a hormone in the absence of any systemic effects.

**Example:** Treatment of atrophic vaginitis with oestrogen creams or pessaries.

### e) The Use of Sex Hormones in Extra-Genital Disorders

The knowledge that sex steroids have non-specific actions (e.g. their effect on the autonomic nervous system, protein metabolism, mineral ion exchanges and organ perfusion) has led to their use in diseases which are not due to endocrine disorder. In these circumstances, high doses of hormone are often employed. In the sexually mature woman, transient menstrual disturbances may occur.

**Example:** 1) Oestrogen or mixed hormone therapy for circulatory disturbances. Combined oestrogen/androgen treatment of osteoporosis.

2) The injection of water-soluble oestrogen compounds for their haemostatic effect on bleeding of extra genital source.

## II. Biological Evaluation and Testing of Hormones

The dosage of a hormone depends not only on the effect desired but also on the variable potency of individual compounds. Steroids, for example, which have been altered by artificial chemical combinations have frequently shown themselves to be unusually potent. In consequence, overdosage is likely if biological activity is not taken into consideration.

Their effect must first be evaluated in animals and only then in humans. Differences in absorption and metabolic breakdown lead to differences in effectiveness. In addition, steroid compounds must be tested in several ways so that unwanted, sex-specific or general actions are not overlooked.

In sections (a) to (c) below, a small selection of tests is listed which are used in the assessment of a newly developed steroid compound prior to its introduction into the therapeutic armoury.

The dosage of steroid hormones, which are chemically pure substances, are expressed in mgs. although it was formally customary to give their biological activity in appropriate units. The latter practice dates back to the time when hormones were obtained in a relatively impure state after extraction from urine rather than by chemical synthesis. The potency of gonadotrophic hormones is expressed in units as their chemical synthesis has not yet been achieved.

### a) Oestrogens

*Peripheral action*:

The biological activity of oestrogens can be determined in castrated animals (rats or mice) and also in ovariectomised women in whom the uterus has been conserved.

A criterion for oestrogen activity in the rodent is the appearance of "oestrus effect" in the vaginal smear (Allen-Doisy test). Between 1933 and 1935, and on the basis of the results of these tests, oestrone and oestradiol benzoate were standardised and measured in IU and IBU respectively. An international unit (IU) of oestrone was defined as 0.1 $\gamma$ of this substance. This is the amount of oestrone which induces a postive "oestrus effect" in 50% of castrated female animals when they receive subcutaneous injections of this substance. The IBU of oestradiol benzoate was defined as 0.1 $\gamma$ of this substance. When oestrone and

oestradiol benzoate are given orally or as implants, different amounts are required to give the same positive tests. A description of their potency in international units is, therefore, no longer valid. The many oestrogens which have been discovered in the years since 1935 have not been standardised in terms of international units. However, from time to time, the number of $\gamma$ or mgs. necessary to bring about oestrus when administered by a certain route has been determined.

The evaluation of oestrogens in ovariectomised humans with an intact uterus forms the basis of the Kaufmann test. In this test, cyclical hormone production by the ovary is mimicked by giving 5 injections of oestradiol benzoate 5 mgs. with 4 days' interval between injections. This is followed by 5, consecutive, daily injections of progesterone 5 mgs. In theory, the oestrogens administered,should cause the proliferative changes normally seen in the endometrium during the early part of a menstrual cycle. Histological examination of the endometrium obtained by curettage can provide evidence of this effect. The behaviour of vaginal epithelium is a sensitive indicator of oestrogen levels. Even small amounts of oestrogen in post-menopausal women with atrophic vaginal epithelium cause karyopyknotic changes so that the intensity and duration of drug-induced oestrogen activity can be determined in this way (Fig. 30). The smear test is particularly suitable for determining the duration of oestrogen effect.

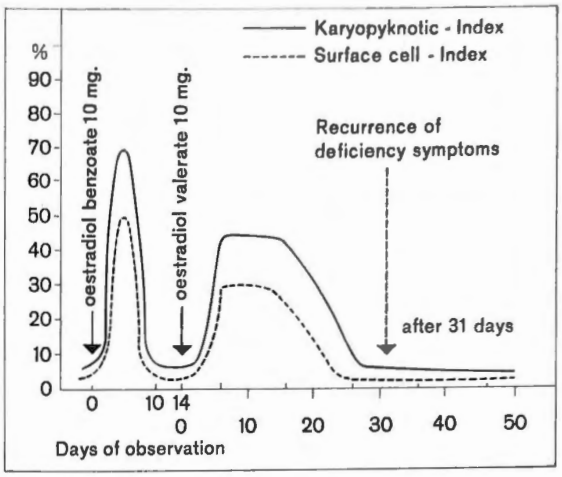



Figure 30. The action of 10 mg oestradiol benzoate and 10 mg oestradiol valerate on the atrophic vaginal epithelium of a woman aged 55 years.
(*Wied, G. L.:* Geburtsh. und Frauenhk. **14**, 45 [1954])

In terms of proliferative endometrial response, individual oestrogens have very different threshold doses and these must be known if a drug is to be used clinically. This dose is not

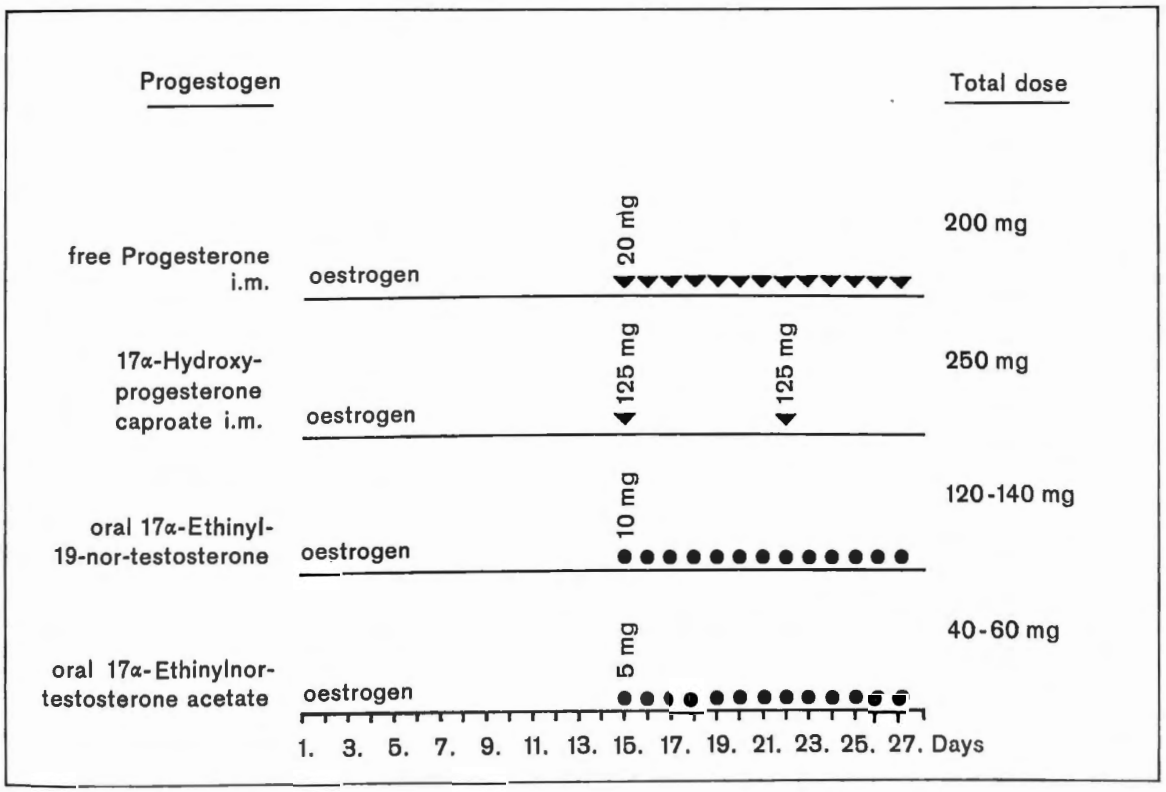



Figure 31. Doses of various progestogens required to induce secretory transformation of an oestrogen-primed endometrium in an ovariectomized subject.

Table 5. *Experimental and clinical methods of testing for Progestogens.*

| Animal tests | Clinical tests |
|---|---|
| Clauberg-Test<br>Deciduoma-Test | Kaufmann-Test<br>Withdrawal bleeding in cases of secondary amenorrhoea<br>Delay of menstruation<br>Examination of changes in vaginal epithelium |
| Proof of local action *(McGinty, Hooker-Forbes)* | — |
| Anti-oxytocin test in pregnant rabbits *(Csapo)* | Anti-oxytocin test with saline terminations *(Bengtson)* |
| Anti-cycle test<br>Anti-ICSH test (reduction in testicular weight) | Quantitative estimation of gonadotrophins in urine<br>Determination of dose level required to suppress ovulation *(Pincus)* |
| Androgenic action on the cock's comb or in the seminal vesicle test | Fructose test |
| Foetal virilisation | — |
| Foetal feminisation *(Neumann)* | — |
| Oestrogenic activity *(Allen-Doisy)* | Effect on vaginal epithelium<br>Estimation of oestrogen metabolites |
| Anabolic action (Levator ani test) | Metabolic balance |
| Anti-ACTH action (measurement of adrenal weight) | Determination of corticoids in urine |

only dependent on the biological activity of a substance but also on its absorption and its inactivation in the liver, particularly when the preparation in question is given orally (see page 12).

*Central action*:

It is desirable to test the anti-gonadotrophic effect of oestrogens on female and male animals. Other methods of testing are also employed (parabiotic experiments or implantation of oestrogens into the spleen).

In humans, the central antigonadotrophic action can be determined by quantitative measurements of excreted gonadotrophin (see page 65) and by the ovulation suppression test (see page 106).

### b) Progestogens

The biological activity of progestogens can be determined experimentally by studying the endometrium of a rabbit. Juvenile or mature castrated females (Clauberg test or the Corner-Allen test) are given oestrogenic hormones in the first instance and subsequently a progestational substance. The degree to which endometrium shows secretory changes is the measure of luteal effect.

The corresponding evaluation in humans can be achieved by means of the Kaufmann test (see page 81). An initial total test dose of progesterone 25 mgs. is not sufficient to evoke premenstrual changes in uterine endometrium. As a result of numerous investigations which compare morphological and functional changes in uterine endometrium with the amount of progesterone produced by the corpus luteum, it would appear that a total dose of 200 mgs. progesterone given over 10—14 days is necessary for normal endometrial development. Information about the doses of other substances required to induce a secretory change are given on page 138.

Progestogens not only evoke secretory changes in endometrium but also have many other actions, some of them desirable and some of them unwanted. The characterisation of any progestational substance should therefore include tests for these additional actions. They should reveal whether an oestrogenic, androgenic, virilising, anabolic, antigonadotrophic or anticorticotrophic effect is exerted. Information of this type is listed in table 5.

### c) Androgens

The potency of androgens may be tested by animal experiments which measure the in-

crease in the weight of the seminal vesicles of a castrated male rat or the enlargement of a cock's comb. The Levator ani test in castrated male rats provides information about the anabolic activity of these substances.

In hypogonadal humans or castrated men, the evaluation of androgens is relatively difficult as it relies on general observations such as the increase in muscle bulk, an increase in sexual potency or observations concerning a subject's general well-being and energy.

In women, the effect of androgens can be tested by cytological studies. The atrophic vaginal epithelium of menopausal women shows proliferative changes in response to testosterone or steroids with an equivalent action.

Another parameter is the measurement of 17-ketosteroids in the urine. Testosterone and its esters are excreted in this chemical form. Repeated measurements after injections of a testosterone compound give some idea about the duration of effect but provide no information about intensity of action. The effect of androgens on protein metabolism can only be determined by balance studies.

### d) Gonadotrophic Hormones

Hypophyseal and chorionic gonadotrophic hormones are standardised in biological units. For these purposes, observations on the gonads of experimental animals are particularly important. In an attempt to make tests more sensitive, infantile or hypophysectomised animals are used. The theory is that their endogenous gonadotrophin secretion is insignificant and thus does not interfere with a biological assay. As the variability of biological responses is rather large it is desirable to carry out tests on large groups of animals (see Table 6).

Table 6. *Nomenclature of gonadotrophic hormones and their characteristic modes of action in hypophysectomised immature rats*

| Abbreviation | name | synonym | site of formation | morphological effect on hyp. imm. rats |
|---|---|---|---|---|
| FSH | follicle stimulat. hormone | — | anterior pituitary | ♀: Stimulation of follicular growth<br>♂: Stimulation of spermatogenesis |
| ICSH | interstitial cell stim. horm. | luteinizing h. (LH) | anterior pituitary | Restitution and stimulation of interstitial cells in the ovary and testes (♀ ♂) |
| LTH | luteotrophic hormone | prolactin, mammotrophin lactogenic hormone | anterior pituitary | ♀: Stimulation of corpora lutea induced artificially by PMS ♂:? and HCG |
| HMG | human menopausal gonadotrophin* | castration gonadotrophin | anterior pituitary | as FSH and ICSH (♀ ♂) |
| HCG | human chorionic gonadotrophin | placental gonadotrophin | placental chorion | similar to ICSH (♀ ♂) |
| PMS | pregnant mares' serum | serum gonadotrophin | placenta of pregnant mares | as FSH and ICSH (♀ ♂) |

* Apparently HMG is a combination of ICSH and FSH.

(*Diczfalusy, E. & Heinrichs, H. D.:* Arch. Gynäk. **187**, 556 [1956])

Follicle stimulating hormone (FSH) only acts in the presence of sufficient amounts of ICSH. In intact or hypophysectomised immature animals, it leads to enlargement of the ovaries or testes. FSH furthers follicular ripening and spermatogenesis. Furthermore, examination of vaginal smears or measurements of uterine weight provide indirect information about gonadotrophic activity. A test in practical use is the estimation of the increase in the testicular weight of hypophysectomised, immature rats treated with HCG.

Luteinizing hormone (LH or ICSH) acts, in the first instance, on the interstitial gonadal cells and also controls luteinization. An exact assay is the increase in weight of the ventral prostate of immature, hypophysectomised rats. Measurement of the ascorbic acid depletion in the ovaries of female rats pretreated with PMS and HCG is another method of assay. It is known as the ovarian ascorbic acid depletion test and was evolved by *Parlow*.

Luteotrophic hormone (LTH or prolactin) is assayed by measuring its effect on the pigeon's crop. It leads to its proliferation and in larger doses to milk secretion by this organ.

Human chorionic gonadotrophin (HCG) is measured by estimating its luteinizing effect on the ovary, or by its effect on ventral prostatic weight. One IU of HCG corresponds to 0.1 mg. of an international standard preparation.

Pregnant mares' serum (PMS), like FSH, is assayed by measuring its effect on the ovaries of immature animals. One IU of PMS corresponds to 0.25 mg. of an international reference preparation.

The results of biological assays for gonadotrophins show considerable variability. The individual characteristics of an animal as well as differences between varying strains considerably influence the reactions in a test situation.

An exact assay of gonadotrophins in humans is not possible.

The purity and hormone content of commercially available preparations (HCG and PMS) in terms of international units per mg. are very variable.

## III. Methods of Administration

### a) Steroid Hormones

Pharmaceutical hormone preparations act in the same way as endocrine gland secretions. It must, however, be remembered that naturally occurring ovarian hormones, are continuously being discharged into the blood stream while injections have a short lived effect with unphysiological peaks of hormone concentration. The duration of action of an exogenous hormone depends on a number of factors which include its absorption, its speed of distribution in the body, its breakdown and its excretion.

*1. Implants*

Although a hormonal implant is a relatively physiological method of administration, it is not now extensively used. Implantation of oestrogen tablets, for example, often led to uterine bleeding which was difficult to control.

The amount of hormone absorbed daily is also very variable as the implant sets up a foreign body reaction and tends to become encapsulated by connective tissue.

*2. Injections*

The intravenous injection of sex steroids only has a limited application as water-soluble esters are rapidly inactivated and excreted. Furthermore, most compounds are unsuitable for intravenous injection because of their poor solubility in water. The use of intravenous water-soluble oestrogens for the treatment of extragenital haemorrhage is somewhat exceptional.

Naturally occurring steroids dissolved in oily media and administered by intramuscular injection have a relatively weak and short-lasting action. Such drugs therefore have to be given on at least alternate days. A longer lasting and stronger action is obtained with derivatives prepared by esterification with fatty acids. At present, many preparations which are easily

Table 7. *Oestradiol and some of its esters. Examples of doses required to build up endometrium and the duration of their effects*

| Steroid | Single dose in mg. | Duration of effect in days | Dose in mg. required to cause endometrial proliferation |
|---|---|---|---|
| Oestradiol | 10 | 2 | 40—60 |
| Oestradiol benzoate | 5 | 6 | 25—35 |
| Oestradiol valerate | 10 | 10—14 | 20 |
| Oestradiol undecylate | 10 | 40—60 | — |

soluble in oil and have a reliable depot action for a matter of days or weeks are available for clinical use. The duration of action is probably a function of an ester's molecular weight. Every depot ester must be tested in animals and also in humans before it is used clinically (see page 42). In calculating dosage, it must be remembered that the time over which a single dose of steroid ester is effective depends, to a certain extent, on the size of the dose (see Table 7).
If it is decided to carry out long-term treatment using depot injections, the interval between injections must not be too great if fairly constant hormone levels are desired.

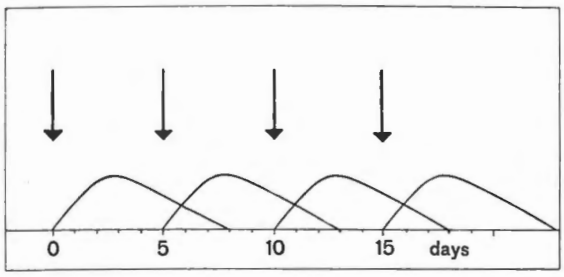



Figure 32. Scheme for treatment with depot injections.

**Example:** Treatment of habitual abortion with Proluton Depot (Primolut Depot). Duration of action: 8—10 days. Interval between injections: 5—7 days.
A depot effect can also be achieved by injecting crystalline hormone suspensions.

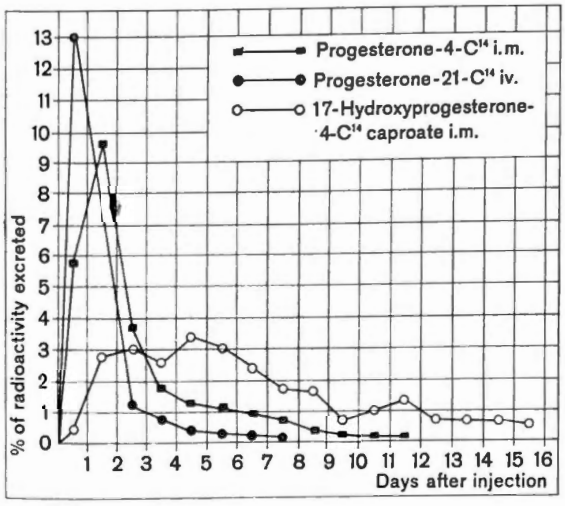



Figure 33. Labelled progestogens and their differing speeds of excretion.
(*Plotz, E. J.*: 6. Symposion der Deutschen Gesellschaft für Endokrinologie, Springer-Verlag 1960, page 21)

This method of treatment gives a depot from which variable amounts of hormone are absorbed daily. The duration of action of a crystalline suspension depends on the actual length of the crystals present.
The size of crystals is limited by the gauge of needles used for injections.

### *3. Oral Therapy*

The naturally occurring steroids, oestradiol, oestrone, progesterone and testosterone, are virtually ineffective in tablet form. After absorption from the small intestine, they are almost entirely inactivated in the liver. They thus never reach their respective end-organs. The hormones' passage through the liver can be circumvented by allowing the tablets to dissolve in the mouth (sublingual or buccal administration). In this way it is possible for naturally occurring sex steroids to exert a definite, but never very marked action.
The search for steroid compounds suitable for oral therapy already showed encouraging results in the 1930's. It was found that substances with an alkyl group at $C_{17}$ had an unusually strong hormonal action. The most widely known example of this is ethinyl oestradiol which is about 100 times as potent as oestradiol (see page 138). The progestogen, 17-ethinyl-19-nortestosterone, and the androgen, 17-methyl-testosterone, are steroids which also belong to this group. In recent years, other potent, orally active compounds have been described. Of these, those with a halogen atom at $C_6$ constitute a particularly interesting group. (Example: $\Delta^6$-6-chloracetoxy-progesterone.) As a result of the large number of well tolerated and effective drugs available in tablet form, most patients are treated by oral therapy, particularly as daily administration leads to constant action over an accurately predictable period of time.

### *4. Local Treatment*

Hormone creams applied to skin and vaginal epithelium have local actions. General effects can also be produced if the amount of hormone administered is sufficiently large and its vehicle is well absorbed. Alcohol and menthol mixtures increase the absorption of a hormone.

### *5. Vaginal Application*

The intra-vaginal use of pessaries, tablets and creams containing hormones is of consider-

able importance. Very small doses of oestrogen cause cellular proliferation with healing of inflamed epithelium.

*6. Rectal Application*

As the inferior haemorrhoidal veins drain directly into the inferior vena cava, suppositories, like buccal therapy provide a method of circumventing immediate absorption and inactivation by the liver.

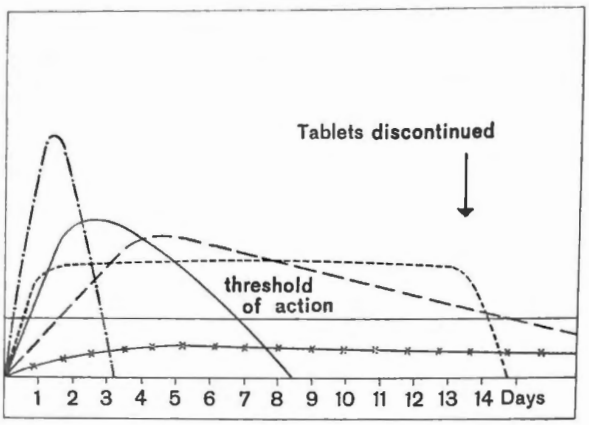



Figure 34. Graph to show the effect with different methods of administration.

——— i.m. injection — — — depot injection
-x-x- hormone implant ····· tablets
—·—·— i.v. injection

### b) Ovarian Extracts

Ovarian extracts which have been recommended for oral therapy contain only small amounts of sex hormone. It has not been proved that they have any therapeutic action. The view that the extracts of whole ovaries might contain substances which are as yet not recognized but still have a beneficial effect on the endocrine system is not one held by clinical or experimental endocrinologists.

### c) Gonadotrophic Hormones

Gonadotrophic hormones (HCG, PMS and the extracts prepared from menopausal urine) have to be administered by intramuscular injection. Oral therapy is ineffective as proteins are broken down in the gastrointestinal tract. Attempts to evolve depot injections of gonadotrophic hormones have, to date, met with no success.

The use of animal pituitary implants as a method of stimulating peripheral endocrine glands has, in most cases, no clinical value. The rapid demise of the implanted gland which can only function in conjunction with the hypothalamus is inevitable. One can only count on slight endocrine gland stimulation, most noticeable in the adrenals during the first days after an implant or injection.

Human hypophyseal extracts contain considerable amounts of FSH and have proved very effective in cases of long-standing amenorrhoea.

## IV. Side Effects of Hormone Therapy and their Prevention

Sex steroids and gonadotrophins, like all effective drugs, have side effects. These are rarely serious as hormones are relatively non-toxic substances. They are the result of actions on certain organs and on the autonomic nervous system. Individuals vary greatly in their sensitivity to these effects. The side effects can be classified as "specific" and "non-specific".

### a) General Non-specific Side Effects

There is gastrointestinal intolerance to certain orally administered steroids, particularly those with a methyl, ethyl or ethinyl group at $C_{17}$. Patients with disturbances of liver function are particularly prone to these gastrointestinal upsets. Should they occur, a change of preparation or drug is advisable. Acute liver changes have been seen with high, non-gynaecological doses of certain steroids with an alkyl group at $C_{17}$ (methyl testosterone, ethyl nortestosterone). This matter is not discussed further here. The intra-gluteal injection of an oily hormone solution occasionally leads to a marked general reaction. It may be that these are actually cases of oil embolism following accidental intravenous injections.

Allergic reactions might be expected in circumstances where animal hormones containing a lot of foreign protein are used. In such cases, a change in the nature of the preparation used may be desirable.

### b) Local Non-specific Side Effects

The repeated intra-gluteal injection of oily solutions can lead to tissue reaction and "oil granulomas". Their occurrence is an indication for discontinuing treatment. Not only do they cause pain but also a reduction in the amount of hormone absorbed.

The almost obsolete practice of implanting hormone pellets often results in foreign body reactions. After an initial inflammatory reaction, the pellets are encapsulated by fibrous tissue so that the release of hormone is diminished or absent.

### c) Specific Side Effects due to Oestrogens

Physiological doses of oestrogen can cause pathological endometrial proliferation if they are administered without the addition of progesterone for more than one month.
When oestrogens are used to treat climacteric symptoms they are particularly liable to cause cystic glandular hyperplasia of the endometrium with resultant metrostaxis. This undesirable effect may be prevented in the following way:
Cyclical oestrogen-progestogen therapy in the sexually mature; small doses of oestrogen combined with androgen as the treatment of choice in the climacterium. Long-acting oestrogens given in depot form or as an implant may be used in women who have had a hysterectomy.
At even low dosage levels, oestrogens inhibit the output of gonadotrophins from the anterior pituitary. Animal experiments suggest that the secretion of FSH is particularly affected. Short-term therapy with appropriate doses of oestrogen at the beginning of a cycle may delay ovulation by several days (see page 93); long-term administration of oestrogens can temporarily suppress ovulation. If the effect on ovulation is not desired, it may be prevented in the following way:
Only small doses of oestrogen should be administered daily during the proliferative phase of the cycle.
As with endometrium, undesired proliferative activity in the breasts may accompany oestrogen therapy, particularly in patients with chronic interstitial mastitis or premenstrual breast tenderness. In such patients oestrogens are generally best avoided.

*General assessment of side effects due to oestrogens:*
The actions on the genital tract are relatively harmless. Although proliferation of the endometrium may cause troublesome bleeding, it regresses as soon as hormone therapy is withdrawn. Similarly, the effect on ovulation is of a transient nature. Potent oestrogens can cause pathological changes in the breasts (mastopathia) which do not regress spontaneously.

### d) Oestrogens and the Formation of New Growths (page 126)

The question of whether or not oestrogens may lead to development of carcinoma in their main target organs, the uterus and the breasts, is much discussed. In purely-bred strains of experimental animal, excessive doses of oestrogens led to tumour formation not only in the organs previously mentioned but also in the kidneys, the epididymis, bone, lymph nodes etc. Whether the information gained in one species, race or breed can be applied to others has always been a matter of some doubt.
There is no clinical evidence which corroborates these animal experimental findings. In humans, the alteration of endocrine balance or the administration of oestrogens cannot lead to the production of carcinoma. In this context it must, however, be remembered that the latent interval between a carcinogenic stimulus and the manifestation of its effect may be one of many years' duration.
The possibility that oestrogens, which cause proliferative activity in nearly all mucous membranes, may enhance the growth of a malignant tumour has also formed the subject of some enquiries. This mechanism, which may be genetically determined, may operate in certain tumours. Relevant animal experiments suggested that oestrogens may be carcinogenic. Confirmatory observations have, however, only very seldom been recorded in human beings.

**Example:** The occurrence of breast carcinoma in a man who has had long-term oestrogen therapy for prostatic carcinoma.

*General Opinion:* Evidence obtained from clinical and experimental investigations does not suggest that intermittent therapy with small doses of oestrogens has any effect on the formation of carcinoma or on the growth of a neoplasm that is already established.

### e) Progestogens

Side effects occur relatively rarely with progestogen therapy. If the amount required to induce secretory changes in proliferative endometrium is exceeded during any one menstrual cycle, morphological changes in the endometrium almost invariably occur.
Endometrial glands become more scanty. Stromal oedema appears. This status is known as "rigid secretion".

If the progestational effect lasts more than 14 days, the appearance of decidual cells may be noted. These cells are normally only seen in pregnancy (see page 31). Pathologists examining endometrial curettings after a course of treatment with progestogens should be told about the latter. If this is not done, an extra-uterine pregnancy may be falsely suspected.
Cyclical progestogen therapy does not usually lead to suppression of ovulation (see page 104). During pregnancy, neither the mother nor the foetus shows signs of progestogen overdosage. However, the literature contains many examples of masculinization of female infants born to mothers known to have had progestogens in the early months of pregnancy. The drugs most commonly responsible were found to be ethinyl-testosterone, ethinyl-nortestosterone and methyl-nortestosterone.

*During pregnancy, unwanted side effects of progestogen therapy can be avoided in the following way:* The exclusive use of progestational steroids which are known to have no virilising action in humans or in animal experiments (e.g. progesterone, 17 α-hydroxy-progesterone caproate).
In the first weeks of pregnancy, only moderate doses should be used (see page 112).

*General opinion about side reactions caused by progestogens:* Side reactions in the sexually mature, non-pregnant patient are of no significance. The virilisation of a female infant after progestogens during pregnancy is to be taken fairly seriously as spontaneous disappearance of the changes induced is unlikely.

## f) Androgens

The following virilising actions of androgens are often seen during treatment (see page 138): excessive hair growth, a coarse skin, deepening of the voice, acne, clitoral enlargement and an increase of libido. In some cases, these changes are not seen even after long term therapy. A patient's constitutional sensitivity to virilising agents as well as her age are of probable significance. The dose of testosterone esters, or methyl testosterone, which has a virilising action, is very different from one individual to another. The duration of treatment is of critical importance. A dose of 400 mgs. testosterone propionate per menstrual cycle is certainly excessive if treatment is continued for a number of months. In such circumstances, even 100 to 200 mgs. testosterone a month may have a masculinizing effect.
After discontinuing treatment, side effects partially regress. While acne and skin changes may disappear rapidly, a deep voice (the result of structural alterations in the larynx) and clitoral enlargement may persist.

*The virilising action of androgens can be minimised in the following way:* Intermittent treatment with androgens only given during the premenstrual phase of patients with menstrual disturbances.
The careful use of androgens in the climacterium. In these circumstances, its combination with oestrogens should be the rule (see page 122).
Androgens are contra-indicated in the first six months of pregnancy.
Androgens, like oestrogens and progestogens (see page 96, 106) may suppress ovulation. However, relatively large doses are required for this effect. (e.g. 2 injections of 250 mg. Testoviron Depot (Primoteston Depot) per menstrual cycle). This dose is seldom indicated.
Patients with advanced mammary or genital tract carcinoma are exceptions (see page 128, 129). Masculinisation must be accepted as inevitable in these cases.

*General opinion about the side reactions to androgens:* Masculinisation cannot always be prevented. This is not difficult to understand if one remembers that this process may often occur spontaneously. Not all the undesirable side effects of treatment regress.

## g) Gonadotrophins

Side reactions with gonadotrophins may be seen in patients with the *Stein-Leventhal* Syndrome whose ovaries are particularly sensitive to their effect. Clinically, painful enlargement of the adnexae occurs.
Ovarian histology shows the formation of haemorrhagic cysts, luteal cysts and also theca cell proliferation. In severe cases, acute abdominal symptoms have led to laparotomy.

*Side reactions to gonadotrophin therapy can be avoided in the following way:* The amount administered per cycle should be restricted to 5,000 units PMS and 15,000 units HCG by intramuscular injection. In cases of *Stein-Leventhal* Syndrome, even these doses may lead to overstimulation of the ovaries (see

page 83). In these cases, not more than 5,000 units of HCG should be administered per menstrual cycle.

### h) Corticoids

Long-term treatment with considerable doses of corticoids (e.g. more than 10 mg. prednisolone per day) may lead to general changes reminiscent of *Cushing's* Syndrome. The main signs are obesity, moon face, the development of striae and osteoporosis. Corticoids have little effect on the female genital tract.
Perforation of peptic ulcers may occur with corticoid therapy. Great care should therefore be exercised when administering this drug to patients with a past history of peptic ulceration.
Pregnancy is no contra-indication to the use of cortisone. Animal experiments have shown that cortisone may induce malformation (growth-inhibition and cleft palates). These findings are however not applicable to the human being.

## V. Concerning the Choice of Preparation

### a) Sex Steroids

Animal experimental and clinical investigations of the limited number of sex steroids mentioned in this text (page 138) have shown that different compounds have a very variable spectrum of action. The focus of interest is the relationship between peripheral and central actions. It follows that it is necessary to try to classify preparations according to the indications for their use if the ideal of effective therapy is to be achieved. In this regard, the potency of a preparation is not as important as its different component actions.

**Examples:**

*1. Ethinyl nortestosterone acetate* is a potent, orally active progestogen. The dose required to transform proliferative into secretory endometrium is 40—60 mgs. In addition, this steroid has a relatively strong anti-gonadotrophic action. A dose of 5—10 mgs. daily may suppress ovulation. Weakly androgenic, anabolic and oestrogenic actions have also been noted with this drug.

*Recommendation:* Suitable for treatment of menstrual disturbances and as an oral contraceptive agent. In these circumstances the androgenic action is not seen.
It should not be used for abortion prophylaxis.

*2. 17α-Hydroxyprogesterone caproate* is a depot progestogen which is entirely free of side actions. The dose required to induce secretory changes in primed endometrium is about 250 mg. per menstrual cycle. The preparation has no significant anti-gonadotrophic action. Suppression or delay of ovulation likewise does not occur.

*Recommendation:* Suitable for treatment directed at preventing miscarriage. Less suitable for cyclical therapy (page 112). Unsuitable as an oral contraceptive progestogen.

*3. Ethinyl oestradiol* is a strong oestrogen. A dose of 0.1 mg. daily for 20 days can provoke physiological proliferative changes in the endometrium of a castrated subject. A dose of 0.075 mg. daily is sufficient to suppress ovulation.

*Recommendation:* Suitable for cyclical and oral contraceptive therapy.

*4. Oestradiol valerate* is an exceptionally well-tolerated depot oestrogen which acts for about 12 days after injection. Two doses of 10 mg. each, on the first and twelfth days of a cycle induce physiological proliferative changes in the endometrium of a castrated subject. The dosage required to suppress ovulation has not been determined.

*Recommendation:* The preparation is suitable for treatment of menstrual disturbances by cyclical therapy, provided that the injections are given at a sufficiently early stage in the cycle.

The four preparations introduced above are those which will be most frequently mentioned in the second half of this book which deals with recommendations for therapy. Naturally, a physician can also achieve successful hormone therapy with other preparations. He should, however, always be fully acquainted with the main effects and the side actions of each compound chosen. This information should further be derived both from clinical trials and from animal experiments.
Very strict criteria must be satisfied before a preparation is used to prevent abortion. Evidence that the preparation has no effect

on the growing foetus is mandatory. The harmlessness of a preparation can only be proved by observing a number of successive generations in animal experiments.

### b) Preparations with Gonadotrophic Actions

The main use of gonadotrophins in gynaecology is to induce ovulation. The ripening of a follicle occurs as the result of the simultaneous action of FSH and ICSH on the ovaries. This combination is found in pregnant mares' serum (PMS).

The same applies to extracts made from menopausal urine (HMG), the only difference being that the latter is of human origin.
Preparations of HCG exhibit almost exclusive ICSH activity.
This knowledge has led to the use of PMS and HMG preparations for their effect on follicular ripening. They are injected on the first eight days of a cycle. Subsequently, HCG is injected in order to bring about follicular rupture. Treatment with a third factor does not appear to be necessary in human beings (further details are given under the heading of Amenorrhoea, page 81).

# H. Diagnosis of Endocrine Disorders

The diagnosis of gynaecological endocrine disorders can be a relatively simple matter. In cases of climacteric menorrhagia or ovulatory bleeding for example, the diagnosis may be strongly suggested by the history. On the other hand, in many cases a satisfactory diagnosis is not possible even with the help of complicated tests such as hormone assays. It must always be remembered that endocrine disorders rarely remain confined to one gland. More usually, there is disturbance of the whole endocrine system, with causes and consequences which may be difficult to sort out. A diagnosis may depend on the history, the results of general and gynaecological examinations and also on many special tests whose practical value and application are very varied.

Table 8. *Summary of diagnostic procedures*

① *Simple measures (no laboratory required)*
- a) history
- b) general and special examination
- c) basal body temperature
- d) diagnostic tests with hormone injections
- e) examination of cervical mucus (no staining required)
- f) endometrial biopsy
- g) hysterosalpingography
- h) X-rays of the pituitary fossa

② *Tests which can be done with simply equipped laboratory*
- a) biological pregnancy test (frog test)
- b) immunological pregnancy test
- c) vaginal cytology
- d) tests of mid brain function
- e) examination of sex chromatin

③ *Clinical tests*
- a) full diagnostic curettage
- b) culdoscopy
- c) exploratory laparotomy

④ *Investigations requiring complicated laboratory equipment. Quantitative estimation of:*
- a) oestrogens in urine
- b) pregnanediol in urine
- c) 17-ketosteroids in urine
- d) gonadotrophic hormones in urine
- e) chorionic gonadotrophin in urine or serum
- f) corticoids in urine

## I. Simple Measures (no laboratory facilities required)

### a) History

Endocrine disturbances may have a hereditary basis. A full family history should therefore be taken. This applies particularly to cases where a serious disorder occurs soon after

birth or during the early years of life. In such circumstances full details about siblings, parents etc. should be taken.

History taking should be suited to the age of the patient and the type of illness suspected. It is naturally important to obtain the following details: age of menarche, menstrual pattern during the early years of sexual maturity, obstetric history, the history of any gynaecological disorders and details about the menopause.

An early menarche usually implies good ovarian and genital tract function, while a late onset of menstruation often means genital tract hypoplasia. If menstrual bleeding does not occur by the age of 18 it is customary to label such a case as "primary amenorrhoea". As women with sterility of ovarian origin often give a history of pubertal menstrual disturbances, they should be questioned about their menstrual pattern during the early years of sexual maturity. At an early age, functional dysmenorrhoea is a common disturbance. Its disappearance after pregnancy is probably due both to maturation of the genital tract and to psychological factors.

*Pregnancy*, *difficult deliveries*, and *miscarriages* often lead to endocrine disturbances. Curettage during the puerperium is of particular importance as it may occasionally lead to complete removal of the endometrium and consequent amenorrhoea. Such amenorrhoea is obviously not of endocrine but of uterine origin. Deliveries which are associated with heavy blood loss may be followed by metabolic disturbances resulting from multiple deficiencies in endocrine gland function.

Menstrual disturbances often occur in the years preceding the climacterium. The benign nature and endocrine origin of certain recurrent types of abnormal bleeding (intermenstrual bleeding at the time of ovulation, pre-menstrual bleeding and bleeding after a menstrual period) may be suggested by the history. Bleeding which is of longer duration and independent of menstruation, on the other hand, immediately arouses suspicion of organic disease. Patients should always be asked about pre-menstrual symptoms as they tend to suppress these as a result of getting accustomed to them over the years. The age of the menopause is of importance in patients with symptoms occurring after the cessation of ovarian function. Even at this age, bleeding may be of hormonal origin. A history of oestrogen therapy may suggest a diagnosis of oestrogen withdrawal bleeding. A hormone producing tumour of the ovary or of the adrenal is much less common.

### b) General and Gynaecological Examinations

*General Assessment*

Endocrine disturbances may cause an alteration in the patient's general appearance or, with congenital disorders, an abnormal phenotype. General consideration of the patient is of utmost importance whenever there is a long history of endocrine disturbance. Virilisation suggests acquired endocrine disease, e. g. adrenal adenoma or arrhenoblastoma. Masculine development of the chest, the muscles and the pelvis, associated with a male hair distribution, suggests congenital disease or disorder (e.g. an intersexual state or adrenal hyperplasia). In the presence of a normal menstrual cycle, moderate degrees of masculinisation are not necessarily pathological and may just represent a constitutional variation. Patients on long-term androgen therapy (e.g. as with breast carcinoma) may show general signs of virilization. In ovarian agenesis, testicular feminization and cases of *Addison's* disease, axillary and pubic hair may be sparse or absent. Dwarfism may be due to ovarian, hypophyseal or thyroid failure. Skin changes may occur with *Cushing'* Syndrome (purple striae), *Addison's* disease (brown pigmentation), pregnancy and with virilization (excess hair).

The recognition of signs indicating endocrine disturbance is as important as a knowledge of the patient's original constitutional build. In addition to the normally developed female, several types of body build are recognized and each tends to be associated with a particular type of endocrine disease.

1. *The Pyknic type.* A normally developed woman often goes over to this type of build after pregnancy or at the end of the years of sexual maturity. This body build is associated with metabolic and endocrine disturbances.

2. *The asthenic.* She may be recognised by the presence of poorly developed female secondary sex characteristics and weak muscular and connective tissue. This type shows no tendency to any particluar type of hormone disturbance.

3. *The Hypoplastic type.* Mental and physical development are incomplete, having been arrested at an earlier stage. This type of patient

shows a tendency to menstrual disturbances such as amenorrhoea or a premature menopause. They also may be sterile.

*Gynaecological Examination*

During gynaecological examination the following should be noted:

Operation scars,
Distribution of pubic hair,
Shape and size of the labia,
The size and elasticity of the vagina,
The nature, macroscopic and microscopic, of vaginal secretion,
The structure of the vaginal vault,
Shape, size and surface area of the cervix,
Macroscopic and microscopic appearance of cervical mucus,
Size, shape, position and mobility of uterus,
State of the ligaments and connective tissue,
Size, shape and mobility of the adnexae with particular reference to the ovaries.

Endocrine disturbances of short duration often cause no genital tract changes. Even so, thorough gynaecological examination is necessary to exclude organic disease. The distribution of pubic hair gives a clue to the patients constitutional type. The development of the labia, the clitoris, and the hymen gives some idea about the degree of genital tract development. The size and elasticity of the vagina and the vault are largely dependent on oestrogenic hormones. The size, shape and consistency of the cervix is of greatest importance. The dependence of the cervix on the general endocrine status is evidenced by its different appearances in pregnancy, during childhood and in hyperhormonal states. The volume and physical characteristics of cervical mucus change. Just before and during ovulation, a copious amount of stringy secretion is found at a gaping external cervical os. The uterus provides various pieces of evidence concerning the presence or absence of hormonal disturbance. A small, sharply anteflexed corpus uteri is associated with an infantile state. A uterus which is normal in size and retro-flexed probably has poor tone which may be the result of ovarian dysfunction. An enlarged uterus may, on the other hand, be found in certain hyperhormonal states (cystic glandular hyperplasia, the pre-menstrual syndrome). The connective tissue reacts in different ways to general autonomic disturbances which in turn may be due to some form of hormonal dysfunction. "Parametropathia spastica" may be a symptom which accompanies disease of the endocrine system. Palpation of the ovaries rarely furnishes evidence of the presence of endocrine disturbance. On the other hand, bilateral ovarian enlargement may be the diagnostic clue to menstrual disturbance which resists hormone therapy (Stein-Leventhal Syndrome). A follicular cyst, though relatively easily palpable in large animals, frequently remains undetected during bimanual examination.

## c) Basal Body Temperature

*How is the temperature taken?*

The temperature should be taken immediately after the patient awakes, before she gets up, before she eats and preferably at the same time every morning. An ordinary clinical thermometer is sufficient for these purposes. The measurement must be exact, be it rectal or oral.
The doctor furnishes the patient with a chart on which she makes daily recordings of the early morning temperature, any menstrual bleeding and any particular or unusual symptoms. The first day of menstrual loss is regarded as day 1 of the cycle and furnishes the signal for starting a new curve.

*When and why does the temperature rise?*

On the 14th to 16th day of a 28 day cycle the temperature rises by about 0.5° C. With the onset of menstruation the temperature again falls. The rise in temperature is due to the action of hormones from the corpus luteum on the temperature regulating centre in the mid brain.

*What is the normal temperature curve in patients who have achieved sexual maturity?*

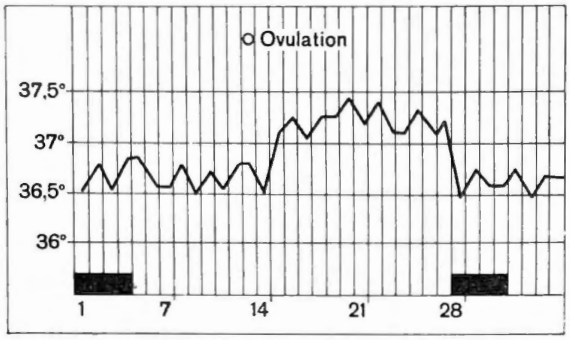
The temperature remains at a lower level during menstruation, in the proliferative phase of the menstrual cycle and up to the time when the ripening follicle ruptures. During the secretory phase of the menstrual cycle when the corpus luteum is functioning, the temperature is elevated by 0.5° C. The temperature curve is thus biphasic.
During pregnancy the temperature remains elevated during the first 3 months (figure 35).

*With what type of endocrine disturbance is the measurement of early morning temperature indicated?*

With all disturbances of the menstrual cycle and with sterility due to endocrine abnormal-

ity, the measurement of temperature is valuable. It provides information about the presence and duration of the two phases of the menstrual cycle. The exact determination of the time of ovulation is not possible as this may occur anything from 1 to 4 days before the rise in temperature. Ovulation, in fact, usually occurs at the lowest point of the temperature curve. Measurements of early morning temperature provide information for the doctor and patient concerning the value of therapy.

Normal biphasic cycle




Pregnancy

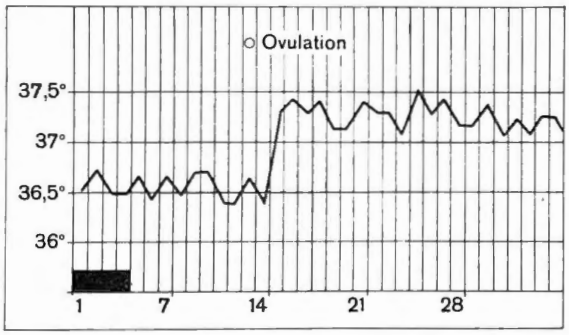



Figure 35. Basal body temperature curve during the cycle and during pregnancy. If the basal body temperature remains elevated for more than 16 days, pregnancy would seem to be likely.

## d) Diagnostic Tests using Hormones[1]

Hormone injections may not only be used as therapy but as a method of furthering diagnosis. They are of particular value in cases of amenorrhoea (page 80).

*1. Which type of hormone injections is of value?*

| | |
|---|---|
| Progesterone | → Progesterone test |
| Oestrogens | → Oestrogen test |
| Gonadotrophic Hormone | → Gonadotrophin test |

[1] *Schrank, P.:* Zbl. Gynäk. **74**, 1569 (1952).

*2. Which type of disturbance can be recognised by the use of hormone injections?*

Grade 1 amenorrhoea (failure of reproductive function of the ovaries).
The exclusion of pregnancy as a cause of amenorrhoea.
Grade 2 amenorrhoea (failure of endocrine and reproductive function of the ovary).

*3. How are the individual tests carried out and what results may be expected?*

α) *Progesterone Test*

In cases of secondary amenorrhoea, menstrual bleeding can usually be brought on by the injection of 20 mg. of progesterone or 1 ampoule of Duogynon (Primodos) on two consecutive days. In such cases the prognosis is favourable.

Progesterone test + = Grade 1 amenorrhoea.

If withdrawal bleeding does not occur, it suggests pregnancy in most cases of short-lived secondary amenorrhoea.
In addition, withdrawal bleeding does not occur in cases of long-standing secondary amenorrhoea with little or no endometrial proliferative activity (Grade II amenorrhoea). The same applies to cases of "uterine amenorrhoea".

| *Progesterone test* | |
|---|---|
| bleeding after 2—8 days | no bleeding |
| amenorrhoea of grade 1 | amenorrhoea of grade 2<br>pregnancy<br>uterine amenorrhoea |

β) *The Oestrogen Test in cases with a negative Progestogen Test*

After pregnancy has been excluded, it must be decided whether amenorrhoea is of the "Grade II" type or the "uterine" type. In this decision, the oestrogen test is of value. It consists of a single, intramuscular injection of 20 mg. Progynon Depot (Primogyn Depot). If bleeding occurs after an interval of between 2—4 weeks, it indicates that the endometrium has undergone proliferative changes, having been atrophic prior to therapy (Grade II amenorrhoea). If no bleeding occurs, "uterine amenorrhoea" is likely. This means that there is no functional endometrium.

| *Oestrogen test* | |
|---|---|
| no bleeding | bleeding after 2 to 4 weeks |
| ∅ uterine amenorrhoea | + grade II amenorrhoea |

*γ) The Gonadotrophin Test*

The prognosis in cases of long-standing secondary amenorrhoea of the "Grade II" type depends, to a certain extent, on the result of a gonadotrophin test. If the ovaries are potentially normal and there is no severe degree of hypophyseal or hypothalamic insufficiency, gonadotrophins may induce ovulation with menstruation after a further interval of 14 days. If this test is positive, it indicates a favourable prognosis.

*Method of performing test:*

3 × 1000 IU Anteron (Primantron) PMS (1st, 3rd and 5th days). Subsequently, 3 × 5000 IU Primogonyl (HCG) (5th, 7th and 9th days).

| *Gonadotrophin test* | |
|---|---|
| biphasic temperature curve | monophasic temperature curve |
| bleeding | no bleeding |
| favourable prognosis | unfavourable prognosis |

## e) Examination of Cervical Mucus

The volume and physico-chemical character of cervical mucus depends on sex hormones[2,3]. Between the 7th and 20th days of the cycle of sexually mature women, crystals form in dried cervical smears, forming the so-called "fern pattern"[4]. This crystallisation does not occur at times when progesterone is being secreted. Thus, ferning is a phenomenon which is not seen during pregnancy and in the pre-menstrual phase of a cycle. The importance of examining cervical mucus can be seen from the following observations:

*1. In non-pregnant women.* If ferning is seen during the pre-menstrual phase of a cycle it indicates that ovulation has not occurred and that no progesterone is being secreted (page 102).

*2. Women with amenorrhoea of short duration.* The presence of a ferning pattern makes pregnancy unlikely. Per contra, the absence of crystallisation suggests pregnancy.

*3. Pregnant patients.* Crystallisation in a cervical mucus during pregnancy indicates some form of hormonal disturbance. It is probable that insufficient amounts of progesterone are being produced[5] (page 111).

*Examination of the cervical mucus for "Spinnbarkeit":* The "Spinnbarkeit" of cervical mucus is the measurement of its viscosity and tensile strength. This varies at different phases of the menstrual cycle. At the time of ovulation, a drop of cervical mucus can be stretched to a length of 8 cms. between two platinum loops.
In the absence of ovulation, this test is negative. It can therefore be used as a simple method for detecting ovulation. The reader is referred to page 102 for details concerning the examination of cervical mucus in cases of infertility.

## f) Endometrial Biopsy

The endometrial biopsy curette may be used for diagnostic purposes without prior dilation of the cervix and without anaesthesia. After preliminary cleansing and disinfection of the vagina and using sterile instruments, this procedure can be carried out in the out-patient department. The endometrium obtained must be placed immediately into a small tube containing absolute alcohol (not formalin). As the damage to the endometrium is minimal, it is possible to repeat endometrial biopsies at appropriate intervals.

*In what sort of disturbances is endometrial biopsy indicated?* Infertility, suspected anovulatory cycles, insufficiency of the corpus luteum and suspected uterine amenorrhoea are all conditions occasionally warranting endometrial biopsy. Histological examination, which includes the microscopic study of tissue treated by special stains, provides information with which it is possible to judge whether endometrium shows secretory changes compatible with adequate corpus luteum function.

[2] *Roland, M.:* Amer. J. Obstetr. Gynec. **63**, 81 (1952).
[3] *Djurisic, S.:* Gynec. et Obstét. **59**, 494 (1960).
[4] *Zondek, B., et al.:* Fertility and steril. **6**, 523 (1955).
[5] *Speck, G., & Halter, P. E.:* Fertility and steril. **7**, 341 (1956).

*When in the cycle is endometrial biopsy carried out?* In the pre-menstrual stage, i.e. between the 24th and 28th days of the cycle. It is also possible to do an endometrial biopsy at the onset of menstruation.

*Can endometrial biopsy replace formal diagnostic curettage?* No. The structure of the endometrium can vary at different points in the same patient and endometrial biopsy is therefore not representative of the whole tissue. If organic disease such as an endometrial polyp or endometrial carcinoma are suspected, full diagnostic curettage is necessary.

### g) Hysterosalpingography[6]

Visualisation of the female genital tract by hysterosalpingography is indicated in cases where it is necessary to exclude a mechanical lesion as a cause of infertility. If hysterosalpingography reveals no organic disease, it is often found that infertility has an endocrine background.
The outline of the uterine cavity gives, or may give, indications of hormonal disturbance. In order to obtain a clear picture of the uterus it is necessary to pull the tenaculum forceps hard down against the canula while the contrast medium is being injected. Water soluble contrast media are preferable[7].

The following findings may be caused by hormonal disturbance:

| |
|---|
| A small uterine shadow<br>→ Hypoplasia of the uterus |
| Irregularity or lack of definition in the outline of the uterine cavity<br>→ Hyperplasia of the endometrium |
| Difficult passage of dye through the Fallopian tubes resulting in their appearance as a stringy shadow on X-ray<br>→ Hypoplasia of the Fallopian tubes |

### h) Skull X-rays

The outline of the pituitary fossa can be visualised by a lateral X-ray of the skull. A diminution in the size of the sella turcica is of no particular significance. At any rate, it is not possible to diagnose pituitary insufficiency on such evidence alone. Enlargement of the pituitary fossa raises the suspicion of a pituitary tumour which can only be confirmed by other investigations.

*When should the sella turcica be outlined by X-ray?* Whenever a pituitary tumour is suspected, particularly in cases where there is a defect in the visual fields. In gynaecology it is important to X-ray the skull in all cases where a disturbed menstrual cycle is associated with the following disorders[8]:

Acromegaly, disturbances of salt or water metabolism,
*Cushing's* disease, growth disorders (infantilism, dwarfism), evidence of abnormal carbohydrate metabolism (a tendency towards hyper- or hypo-glycaemia),
Obesity or severe anorexia, marked disturbances of sexual function (amenorrhoea, persistent lactation).

## II. Investigations Requiring Modest Laboratory Equipment

### a) Biological Pregnancy Test (Frog Test)

*Principle underlying test.* The injection of gonadotrophins or chorionic gonadotrophin, found in pregnancy urine, leads to transient shedding of sperms by the male toad or frog.

*Technical details.* For the diagnosis of pregnancy, 1—2 ml. of fresh morning urine, or better still serum, are injected into the dorsal lymph sac of the frog. After only one or two hours, a small drop of fluid can be aspirated from the cloaca using a pipette. This fluid can be examined microscopically without fixing or staining. If sperms are found, this indicates a positive test.

Tested in this way, the production of sperms continues for some 36 hours. At least 3 frogs should be used for each test.

*Earliest confirmation of pregnancy.* The amount of chorionic gonadotrophin in the urine is sufficient for a positive result 10 days after the first day of the first missed menstrual period.

*Sensitivity of the frog test.* Experiments with corresponding hormone preparations have shown that about 20—30 IU of chorionic gonadotrophin are necessary to stimulate the release of spermatozoa. The reliability of the

[6] *Schultze, G. K. F., & Erbslöh, J.:* Gynäkologische Röntgendiagnostik, Stuttgart 1954.
[7] *Erbslöh, J.:* Röntgen-Bl. 7, 1 (1954).
[8] *Zondek, H.:* Krankheiten der endokrinen Drüsen, Basel 1953.

test depends on the season and the temperature at which the frogs are kept. Between July and October, they show a particularly marked reduction in response to injected hormone.

*Increasing the sensitivity of the test.* Shaking the urine with ether removes some toxic substances. A frog can tolerate up to 10 ml of urine cleansed in this way. By this measure, the sensitivity of the test may be increased by a factor of 5.

*Negative tests with ectopic pregnancies.* As soon as an ectopic pregnancy dies, the amount of chorionic gonadotrophin excreted in the urine falls. If some time has elapsed since the death of the ovum, the frog test may be negative, particularly in cases of tubal abortion (see *Hartleb*[9]). In cases of suspected ectopic pregnancy, therefore, it is best not to rely on the results of the Galli-Mainini test but to use more sensitive tests such as the AZ-reaction or the rat smear test (page 66).

*A semi-quantitative frog test*[10, 11]. By injecting up to 10 ml. of ether-treated urine or using only small or diluted amounts of urine, it is possible to determine a dilution at which the pregnancy test is still only just positive. If the sensitivity of the animals to chorionic gonadotrophin is known and allowance is made for the amount of urine excreted in 24 hours, it is possible to give a semi-quantitative value for the gonadotrophic hormone content of the urine being examined (pages 65 and 66).

### b) Immunological Pregnancy Tests

Immunological pregnancy tests are based on the detection of chorionic gonadotrophin in the urine with the aid of specific antibodies to this protein hormone (*Wide-Gemzell*[12]). The anti-serum necessary for the test is obtained from rabbits sensitized by serial injections of HCG. In order to carry out the test, HCG-coated sheep's red blood cells (Pregnosticon) or similarly coated latex particles (Ortho) are necessary.

*Performance of the Pregnosticon tests* — 0.1 ml. of urine and 0.4 ml. of HCG-coated red cells are added to the antiserum, shaken and allowed to stand for a period of 2 hours. With negative reactions, the suspension of red cells remains undisturbed and uniformly opaque. In positive reactions, the agglutinated red cells are deposited as a red ring at the bottom of the test tube.

*Performance of the Ortho tests* — A mixture of 0.5 ml. of anti-serum and 0.5 ml. of centrifuged urine is allowed to stand for 1 hour at 37° C. After the addition of 1.0 ml. of latex particles in suspension, a further incubation at 37° C. for 2 hours is made. The whole mixture is centrifuged for 2 minutes. The reaction is negative if, after centrifugation, there is a well-defined precipitate with supernatant fluid which is clearer than the standard suspension. If, however, HCG is present in the urine, the antibodies are neutralised during the first hour of the test and agglutination of the latex particles cannot, therefore, occur.

Thus, no sediment forms and the solution is uniformly opaque after centrifugation. The rapid slide test for pregnancy is based on the principle of the Ortho test.

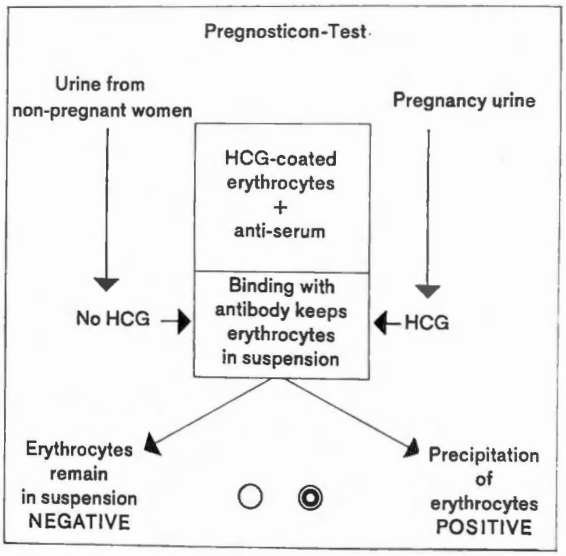



Figure 36. Diagram to show the principle and method underlying the Pregnosticon pregnancy tests. (*Lauritzen, C.:* Dtsch. med. J. 14, 644 [1963])

With regard to opacity of solutions, the two tests described are contrary! With regard to sensitivity and reliability, the immunological tests are superior to the biological tests. Thus, the former may give positive results in cases of extra-uterine pregnancy, although the amounts of HCG being excreted are rather low. The speed of immunological tests and the fact that no animals are required for their performance are further advantages in their

[9] *Hartleb, H.:* Geburtsh. u. Frauenhk. 13, 525 (1953).
[10] *Hartleb, H.:* Geburtsh. u. Frauenhk. 11, 938 (1951).
[11] *Risse, T.:* Geburtsh. u. Frauenhk. 16, 1112 (1956).
[12] *Wide, L., & Gemzell, C. A.:* Acta endocr. 35, 261 (1960).

favour. A comparison between biological and immunological tests is made on page 66. With immunological testing, synthetic agents used for the cleansing of glassware and accidental agitation of the reagent tubes at times when they should be incubating, may introduce errors. Menopausal urine may show a weakly positive reaction, a fact which may give rise to some confusion[13,14]. The results are often positive in patients with neoplasms. There is thus some doubt about the specificity of immunological methods[13,14a].

### c) Vaginal Cytology[15,16]

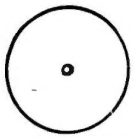
Vaginal smears can only be used for diagnostic purposes in circumstances where specialist knowledge is available, and the latter demands a considerable period of specialised training. Fixing and staining of the smears must be carried out with care so that an experienced cytologist can give reliable interpretations of the material he examines.

*Preparation of the smear*[17]. After visualising the vaginal vault, a small amount of vaginal secretion is removed from the posterior or lateral walls using a wooden spatula. A smear of this material is made on a glass slide. Unlike cytology used for cancer detection, secretions can be taken from the surface of the portio vaginalis or from the cervical canal. In order to obtain a reliable diagnosis, it is important to prevent cell changes due to artefact. After the smear has been made and before it has had a chance to dry, the slide should be immersed in a mixture containing equal parts of 96% alcohol and ether for at least half an hour to allow time for proper fixation. Subsequently, the smear should be stained according to the method of Papanicolaou.

The smear may be stained more simply using acridine orange and fluorochrome. The subsequent appearance of cells is such that accurate diagnosis is possible[18]. In describing the appearance of a smear, the simple method of grading used by *Schmitt*[19,20] may be used, although it does not attach as much importance to the description of leucocytes or bacteria as it does to the folding and distribution of epithelial cells. If the cell proliferation observed is grade 4 or grade 3, an oestrogenic stimulus is implied. A grade 2 or grade 3 picture indicates stimulation by androgenic hormones in the absence of oestrogens[21] (androgen-proliferation[22]). Progesterone alone causes hardly any proliferation[23]. The simultaneous presence of oestrogens, a synergism which always exists in the natural state, results in the transformation of a grade 3 or 4 slide into one which is grade 2 to 3. Thus progestogens, in common with their action on the endometrium, have an "antiproliferative" effect on the vaginal epithelium.

Fig. 37. *Normal cells in the vaginal smear*

Apart from leucocytes and bacteria 4 main types of cells can be found in the vaginal smear.[20]

| | |
|---|---|
|  | Cornified, superficial squamous epithelium (pyknotic nucleus, mostly acidophilic plasma, platelike cells mostly with a well circumscribed periphery). |
| | Uncornified superficial squamous epithelium (vesicular nucleus, basophilic plasma, more frequently folded cells, cell borders mostly well defined). |
| | Intermediary cells (small cells with a relatively big vesicular nucleus, basophilic plasma, folded cells, frequent conglomeration of cells, cell border sometimes not clearly defined). |
| | Parabasal cells (small cells with a relatively large nucleus frequently with a distinct anisonucleosis and anisocytosis, rare folding of cells, no conglomeration of cells; frequent atypical stain). Genuine basal epithelium is very rarely observed. |

[13] *Hohlweg, W.:* Wien. med. Wschr. 113, 687 (1963).
[14] *Richter, R., & Arnold, M.:* Ärztl. Lab. 9, 194 (1963).
[14a] *Tensen, V., & Støa, K. F.:* Nordisk Medicin 73, 433 (1965).
[15] *Zinser, H.-K.:* Zytodiagnostik in der Gynäkologie, Jena 1951.
[16] *Igel, H.:* Gynäkologische Zytodiagnostik, Walter de Gruyter & Co., Berlin 1959.
[17] *Boschann, H.-W.:* Technik der gynäkologischen Zytodiagnostik, Walter de Gruyter & Co., Berlin 1961.
[18] *Dubrauszky, V., & Jäger, J.:* Med. Welt 1962, 1359.
[19] *Schmitt, A.:* Geburtsh. u. Frauenhk. 13, 593 (1953).
[20] *Wied, G.:* Röntgen-Laborat.praxis 6, 209 (1953).
[21] *Boschann, H.-W.:* Arch.Gynäk. 187, 39—64 (1955).
[22] *Wied, G.:* Ärztl. Wschr. 7, 844 (1952).
[23] *Rauscher, H.:* Münch. med. Wschr. 94, 2158 (1952).

A further characteristic of the smears is the appearance of leucocytes and slightly basophilic cells with folded edges[24].
In the sexually mature woman, only the first 3 types of cell are found. Their relative amounts depend on the phase of the menstrual cycle at the time of the smear. Acidophil cells with a pyknotic nucleus predominate during the follicular phase of the cycle. Epithelial cells with rolled edges and larger nuclei are found during the luteal phase of the cycle. Intermediate cells occur during menstruation. With declining ovarian function, parabasal cells may appear. In the markedly atrophic state, these cells may be found to the exclusion of all others and they sometimes occur in aggregates. The smear in normal pregnancy shows mainly intermediate cells which are also known as navicular cells (page 111).

In interpreting a smear, the following factors should be considered[20]:

1) The age of the patient.
2) The date of the last normal menstrual period.
3) The menstrual history, particularly in cases of irregular dysfunctional bleeding.
4) Treatment with hormones.
5) Previous intravaginal therapy or douches.
6) X-ray or radium treatment.
7) Inflammatory lesions of the genital tract.

In certain circumstances, a number of smears taken at intervals and over a period of time may be necessary to obtain a true picture of hormonal status. In circumstances where inflammation of the vaginal epithelium makes it impossible to interpret a smear accurately, a course of treatment with the appropriate antibiotic is necessary.

*Which disorders can be diagnosed with the aid of vaginal smears?*

As each phase of the menstrual cycle is associated with a characteristic type of smear, hormonal disturbances may frequently be recognised by means of these tests. The vaginal smear may also provide evidence with which it is possible to assess whether a disorder is due to an excess or deficiency of hormones (e.g. amenorrhoea, suspected hormone producing tumours).

[24] *Burger, H., & Roth, O. A.:* Gynaecologia **132**, 111 (1952).

*What are the relative merits of diagnostic curettage and endometrial biopsy?*

The vaginal epithelium is a sensitive indicator of oestrogen activity. The fact that vaginal smears can be repeated at short intervals is the main advantage they carry. The action and duration of local hormone applications can be assessed without difficulty in this way. Equally, hormone dosages (e.g. treatment with gonadotrophins) can be judged in this way.
The endometrial response to hormonal stimuli is somewhat slower. Histological examination of the endometrium treated with stains which are specific for glycogen and phosphatase may give a much more accurate and detailed picture of hormonal status. The main disadvantage of studying the endometrium is the fact that neither endometrial biopsy nor diagnostic curettage can be repeated too frequently.

### d) Assessment of Hypothalamic and Anterior Pituitary Function

The hypothalamic-anterior pituitary-ovarian axis constitutes a functional unit which has close connections with other endocrine glands and also with the brain[25, 26] and the autonomic nervous system. The hormones produced by the ovary can be determined with relative certainty by quantitative measurements of the sex hormone metabolites in urine.
The measurement of gonadotrophins in urine, on the other hand, does not provide accurate information about the function of the hypothalamus or the anterior pituitary. In circumstances where endocrine disturbances of central origin are suspected, it is necessary to undertake tests to measure hypothalamic function.
It must be remembered that the hypothalamus is not only associated with gonadotrophic activity but also influences, both directly and indirectly, water balance, protein and carbohydrate metabolism. It is thus necessary to employ tolerance tests which are designed to measure these different functions.

1. The formation and excretion of gonadotrophic hormones can be approximately estimated by their measurement in urine (page 65).

[25] *Hohlweg, W., & Junkmann, K.:* Klin. Wschr. **11**, 321 (1932).
[26] *Westman, A., & Jakobsohn, D.:* Acta obstetr. gynec. Scand. **17**, 235 (1937).

2. Water metabolism may be assessed by a water load test. A thirsting subject who ingests 1,500 ml. of fluid should, under normal circumstances, excrete this volume within four hours. The excretion of an amount below 600 ml. is pathological. Pitressin (hypophysin) has an anti-diuretic effect which inhibits this excretion. Delayed water excretion suggests hypothalamic disturbance as does an abnormal response to the injection of Pitressin (hypophysin).

3. To obtain a picture of protein metabolism, cumbersome balance studies are necessary. In this connection, the specific dynamic action of protein is of particular interest. To determine this, oxygen consumption is measured first while a subject is starving and then 30, 60, 90, 120 and 150 minutes after the ingestion of 200 g. of protein in the form of meat. Normally, oxygen consumption increases by 20—40% roughly one hour after the ingestion of the standard meal. If the response is absent or excessive a disturbance in the function of the mid brain is suggested.

4. Carbohydrate metabolism (the tolerance test designed by *Staub-Traugott*). The administration of 50 g. glucose leads to transient hyperglycaemia with blood sugar values of 160—180 mg.% after 30—60 minutes. The further ingestion of 50 g. of glucose after an interval of 90 minutes is not associated with a further increase in blood sugar levels in a healthy subject. The hyperglycaemic phase is followed by reactive hypoglycaemia with a fall in blood sugar to 70 to 90 mg.% (a positive Staub-Traugott test). The test is abnormal if the blood sugar continues to rise after the second dose of sugar has been given, or if there is no reactive hypoglycaemia.

*Insulin tolerance test.* For each 6.5 kg. of body weight, one unit of soluble insulin is injected intravenously and the blood sugar is measured after 10, 15, 20, 30, 60, 90 and 120 minutes. In normal circumstances, this leads to hypoglycaemia with blood sugar values of 20 to 40 mg.% after 20—30 minutes; the blood sugar returns to normal after 80 minutes. Lack of sensitivity to insulin is as pathological as prolonged hypoglycaemia. In both circumstances an abnormality of carbohydrate metabolism may be suspected.

*The adrenaline test.* Adrenaline 1 mg. is injected subcutaneously. Subsequently the blood sugar is estimated at 5 minute intervals while leucocyte counts are carried out at 10 minute intervals. After 20—60 minutes, a leucocytosis occurs, together with a rise in blood sugar to levels which are twice as high as the resting values. The blood pressure also rises by about 50%. After 120—180 minutes these changes are no longer detectable. In circumstances where there is disorder of the autonomic nervous system due to insufficiency of the hypothalamus (hypo-regulatory type) the blood sugar, blood pressure and leucocyte counts are not much influenced by the injection of adrenaline. An excessive response indicates hypothalamic disturbance of the hyper-regulatory type.

*With what disorders is it advisable to investigate the function of the hypothalamus?*[27]

*Cushing's* Syndrome,
Acromegaly,
Dystrophia adiposogenitalis,
Obesity or anorexia nervosa,
Diabetes insipidus,
Amenorrhoea of anterior pituitary origin,
Growth disturbances of anterior pituitary origin,
Severe and persistent climacteric symptoms which cannot be influenced by treatment,
Disturbances of water metabolism which are not associated with cardiac or renal lesions.

### e) Examination of Sex Chromatin

Sex chromatin or the "*Barr*" body[28] is the hallmark by which cells from all types of female tissue can be recognized. Microscopically, it is an easily recognized, sharply outlined, basophil structure lying on the inner surface of the nuclear membrane. The frequency with which Barr bodies occur in females lies between 20 and 60%. In men, it is only found in 0—5% of all cells. The presence of the Barr body depends on the existence of two X chromosomes (the normal sex chromosome constitution, see figure 11, page 25).

*Technique:* A smear is taken from the buccal mucosa with a spatula and after it has been spread on a glass slide it is immediately fixed in a solution containing equal parts of 95% alcohol and ether for at least 30 minutes.

[27] *Damm, G.:* Dtsch. med. Wschr. **75**, 1016 (1950).
[28] *Barr, M. L., & Bertram, E. G.:* Nature **163**, 676 (1949).

Subsequently, the smear is best stained by the method of Papanicolaou.
The "drumsticks" or "sessile nodules" which occur in segmented polymorphonuclear leucocytes of women provide a further method of sex determination by histological means. It is not absolutely certain whether these nuclear appendages are identical with sex chromatin. They occur in only 1.5—5% of polymorphs. In men, they are not seen at all.

*Technique:* 500 leucocytes are examined in a blood smear stained by *Giemsa*. The presence of six or more cells showing "drumsticks" or "sessile nodules" indicates that the patient is female[29].
Blood cultures for chromosome analyses are much more difficult and time-consuming. They are mainly used for scientific purposes and require either venous blood or bone marrow.

*In what sort of cases should sex chromosome determinations be carried out?*[30, 31, 32]

1. Suspected *Turner's* Syndrome: most of these show the male picture (page 87).
2. Primary amenorrhoea: about one-third show a male sex chromatin pattern (page 77).
3. Testicular feminization syndrome: in typical cases, the sex chromatin pattern is male (page 99).
4. The adreno-genital syndrome: in most cases the sex chromatin pattern is female (page 84).
5. Pseudohermaphrodites: no characteristic sex chromatin pattern (page 99).
6. *Klinefelter* Syndrome: female sex chromatin pattern (page 99).
7. Cryptorchidism: male sex chromatin pattern. A female sex chromatin pattern suggests a diagnosis of Klinefelter's Syndrome.

In cases where there is retarded development or malformation, these investigations may also be indicated. They frequently reveal the underlying cause of such a disturbance.

[29] *Davidson, W. M., & Smith, D. R.:* Brit. med. J. 4875, 1379 (1954).
[30] *Prader, A., & al.:* Schweiz. med. Wschr. 85, 1085 (1955).
[31] *Bergemann, E.:* Schweiz. med. Wschr. 92, 1253 (1963).
[32] *Hienz, H. A.:* Geburtsh. u. Frauenhk. 23, 891 (1963).

## III. Clinical Investigation

### a) Diagnostic Curettage[33]

In contra-distinction to endometrial biopsy (page 55), diagnostic curettage is a hospital, in-patient procedure requiring general anaesthesia. Curettage provides not only a method of diagnosis but also, sometimes, a form of treatment. In the sexually mature woman, repeated curettage is not advisable in circumstances where a diagnosis has been established. With recurrent menorrhagia in young women, repeated diagnostic curettage is contra-indicated as it may lead to endometrial damage and difficulties during subsequent deliveries.

*In what sort of circumstances is diagnostic curettage indicated?*

The main indication is abnormal bleeding with a clinically normal genital tract. Decisions about the treatment of abnormal bleeding must always depend on the results of curettage and histological examination of the endometrium. By these means, any of the following disorders may be recognized:

1. Organic disease of the genital tract (carcinoma, fibroids, endometrial polyps and abortions).
2. Functional disorders (e.g. cystic glandular hyperplasia) or
3. Inflammatory lesions (e.g. endometritis, tuberculosis etc.).

Although diagnostic curettage cannot influence its underlying cause, dysfunctional bleeding may improve after operation. Recurrences of abnormal bleeding may, however, occur. In such cases, treatment with hormones often becomes necessary (page 90).

*When should curettage be carried out?*

Just as with endometrial biopsy, diagnostic curettage should be undertaken in the premenstrual phase if there is no urgency.

### b) Culdoscopy[34]

The introduction of a culdoscope into the pouch of Douglas through the posterior vaginal fornix with a patient in the knee-chest position allows direct inspection of the uterus, tubes and particularly the ovaries. In most

[33] *Lau, H., & Stoll, P.:* Landarzt 39, 719 (1963).
[34] *Antonowitsch, E.:* Arch. Gynäk. 178, 64 (1950).

cases, an experienced observer can estimate the size and can observe the surface of the ovaries quite accurately. The presence or absence of a corpus luteum cannot, however, be detected with certainty. The main indications for culdoscopy are disturbances of ovarian function which are resistant to treatment (e.g. primary amenorrhoea or suspected *Stein-Leventhal* Syndrome). Culdoscopy may also be of value in cases of endometriosis which are treated conservatively.

### c) Exploratory Laparotomy

Exploratory laparotomy is only seldom indicated.

It is recommended in cases where culdoscopy fails to provide sufficient information about ovarian failure, an inter-sexual state or the presence of possible malformations[35]. The decision to operate can be made more easy by the presence of a mass or of appendicitis. Inspection of the ovaries alone may not provide sufficient information about the nature of a disorder. Wedge biopsies with histological examination of the material obtained may therefore be indicated.

## IV. Investigations Requiring Complex Laboratory Equipment

(Hormone Assays)

It is proposed to discuss urinary hormone assays quite briefly here. In order to give a firm opinion about the nature of hormonal disturbances it is almost always necessary to carry out repeated hormone assays.

*Loewe*[36] was the first to demonstrate the presence of substances with hormonal activity in urine. To begin with, biological assay methods such as the cock's-comb test[37] for androgens and the oestrus test of *Allen-Doisy*[38] for oestrogens were used. The results were expressed in biological units. The first chemical hormone assays were made by *Kober* (phenol-sulphuric acid reaction for the measurement of oestrogens)[39] and by *Zimmermann* (the estimation of 17-ketosteroids)[40].

At the present time, all hormones whose chemical structure is known, are measured by chemical methods and the results are expressed in mgs. The gonadotrophins constitute an exception but their exact chemical composition is not yet known. They are measured by biological or immunological methods. The particular advantage of chemical assay methods is that they measure both the hormone and its related metabolites without regard to their biological activities.

In interpreting the results of hormone assay in urine[41], it must be remembered that one is measuring substances which are predominantly metabolites of endocrine gland secretions. Allowance must also be made for the fact that only a proportion of any hormone administered is recovered in urine.

It is probable that considerable amounts of hormone are broken down into chemical fragments which are not measurable by biological or chemical methods. Where 24-hour specimens of urine are concerned, it is important to make sure that they have been carefully collected, adequately mixed and measured and that a sufficiently large aliquot is used for the ultimate hormone assay. Cold storage or the addition of chemicals (e.g. Toluol) may be necessary in order to prevent deterioration and degradation of urine before its examination.

Steroids are excreted in water-soluble form (as sulphates or glucuronides) in urine. In order to extract the hormones it is necessary to make them insoluble in water. This can be achieved by hydrolysis and the manner in which this hydrolysis is carried out depends on the steroid being measured. Subsequently the extraction is completed with the aid of organic solvents. The urinary extracts contain a mixture of about 60 different metabolites which together account for a total of 40 to 70 mg. in a 24-hour specimen. The separation of individual hormonal substances from this mixture is known as the process of fractionation.

The first separation is into acid and neutral substances. Subsequently, the phenolic steroids (oestriol, oestrone and oestradiol) are separated from the neutral substances. The latter are further separated into ketones and non-ketonic substances.

[35] *Philipp, E.:* Dtsch. med. Wschr. **78**, 286 (1953).
[36] *Loewe, S.:* Klin. Wschr. **4**, 1407 (1925).
[37] *Moore, C, & al.:* Endocrinology **13**, 367 (1929).
[38] *Allen, E., & Doisy, E. A.:* J. Amer. Med. Ass. **81**, 819 (1923).
[39] *Koebr, S.:* Biochem. Zschr. **239**, 209 (1931).
[40] *Zimmermann, W.:* Zschr. phys. Chem. **233**, 257 (1935).
[41] *Loraine, J.:* The clinical application of hormone assay, E. & S. Livingstone, Edinburgh & London 1958.

For details of methodology one should refer to the original article[42].

### a) Oestrogens in Urine

The oestrogenic activity of urine can be tested biologically on castrated animals and the results can be expressed as biological units. However, by chemical methods, oestradiol, oestrone and oestriol can each be measured separately and quantitatively. Brown's method[43] is particularly exact but requires a considerable amount of laboratory equipment. As little as 4 γ of oestrogen may be detected. The values obtained are, however, often lower than those with other methods. Simpler methods, e.g. the one designed by *Ittrich*[44], are probably equally satisfactory.

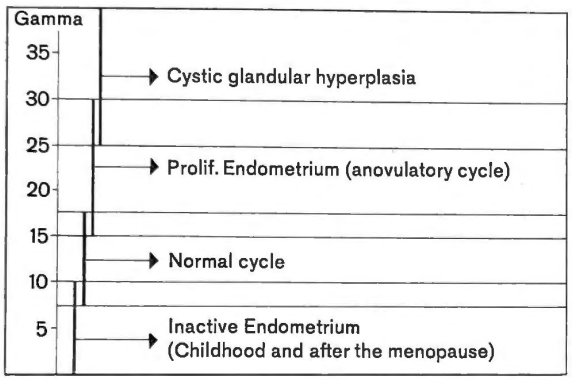



Figure 38. Average total oestrogen excretion in γ. (*Brown, J. B., & Matthew, G. D.*: Recent Progr. Hormone Res. **18**, 363 [1962])

In the *sexually mature woman*, the excretion of oestrogens varies during the different phases of the menstrual cycle[45]. In the first days, about 5 γ of oestrone as well as oestriol are found. The oestradiol values are always lower. The amount of hormone excreted rises and reaches a maximum on about the 12th day when some 20—30 γ of each hormone can be measured. After a transient fall in the amount excreted, a second post-ovulatory peak is reached on the 20—22nd day. Premenstrually, the values fall again so that the lowest values for 24-hour urinary oestrogen excretion are obtained during an actual menstrual period (figure 16, page 28).

*Pregnancy.* After fertilisation, there is no premenstrual decrease in oestrogen excretion[46]. Instead, an initially gradual and subsequently rapid rise of oestrogen excretion occurs until the twenty-fifth week of pregnancy. At this time, considerable amounts of oestrogen are excreted: about 40 mg. of oestriol (!), a little over 1 mg. of oestrone and 0.4—0.5 mg. of oestradiol per day. A gradual increase of hormone excretion continues during the last week of pregnancy and after delivery the levels fall again within a matter of several days (see figure on page 34).

Contrary to what was previously thought, women still excrete oestrogens after the menopause and the urine contains detectable levels of oestriol and oestrone. The values stay between 4 γ and 8 γ per 24 hours.

These hormones only disappear from the urine if the ovaries and adrenals are removed, as in some cases of inoperable breast cancer. If, as occasionally happens, traces of hormone are still found after this type of surgery, they probably stem from the patient's diet.

*Does the estimation of oestrogens have diagnostic value?*

In most circumstances, the complicated laboratory equipment required for Brown's method is unnecessary as both vaginal cytology and endometrial biopsy are two simple tests which supply sufficient information about oestrogen activity.

In the following disorders, repeated chemical oestrogen estimations are of clinical and academic interest[47]:

1. Amenorrhoea (page 78),
2. Cases in which a hormone producing tumour is suspected (page 131, 133),
3. Premature labour (page 112),
4. Cystic glandular hyperplasia (page 89),
5. Breast carcinoma (page 126).

### b) Pregnanediol in Urine

The progesterone content of body fluids can be measured by chemical and biological methods. As these methods are hardly ever used for diagnostic purposes they will not be described in any detail here. Pregnanediol is the biologically inactive, excretory metabolite of progesterone. In amounts exceeding 1 mg., it can be accurately measured chemi-

[42] *Zimmermann, W.*: Chemische Bestimmungsmethoden von Steroidhormonen, Springer-Verlag 1955.
[43] *Brown, J.*: Biochem. J. **60**, 185 (1955).
[44] *Ittrich, G.*: Hoppe Seyler's Zschr. physiol. Chem. **312**, 1 (1958), Zbl. Gynäk. **82**, 429 (1960).
[45] *Brown, J.*: (1955) Lancet, I, 320.
[46] *Brown, J.*: (1956) Lancet, I, 704.
[47] *Diczfalusy, E.*: Bull. Soc. Roy. Belge Gynec. Obstétr. **30**, 267 (1960).

cally by the method of *Klopper*[48]. When calculating the amount of progesterone produced, it must be remembered that only about 14% is excreted as pregnanediol in urine.

Except for small amounts of hormone which probably originate from the adrenals (page 28), significant amounts of pregnanediol are only found in the urine during the second half of the menstrual cycle[49]. Just before ovulation, the excretion of pregnanediol begins to increase and reaches its maximum values between the 18th and 24th days of the menstrual cycle. During these days, about 2.5 to 5 mg. are excreted in a 24-hour period. The excretion of pregnanediol diminishes again during the pre-menstrual phase.

Hardly any pregnanediol is found during menstruation. The amount of pregnanediol excreted in the urine during the secretory phase of a menstrual cycle suggests that a single corpus luteum secretes 200 mg. of progesterone during its life-span (see figure 17 page 29).

Should pregnancy occur, pregnanediol excretion rises steadily. The increase continues until the end of pregnancy so that in the fifth month of gestation about 30 mg. are excreted, and at the end of pregnancy about 100 mg. of pregnanediol can be recovered from a 24-hour urine[51].

*Does the measurement of pregnanediol excretion have any diagnostic value?*

In clinical practice, the use of this method is not often indicated. The function of the corpus luteum and its secretion of progesterone can be deduced from basal body temperature curves, examination of vaginal smears, "ferning tests" on cervical mucus and histological examination of the endometrium. All these procedures are simpler than the measurement of pregnanediol excretion. With the following disorders, the repeated estimation of pregnanediol excretion may be of some value:

1. Amenorrhoea (page 78),
2. Cases in which adreno-genital syndrome is suspected (page 84),
3. Cases of infertility (page 104),
4. Threatened abortion (page 111).

[48] *Klopper, A., & al.:* J. Endocr. **12**, 209 (1955).
[49] *Dibbelt, L.:* Zschr. Geburtsh. **132**, 58 (1950).
[50] *Ober, K. G.:* Geburtsh. u. Frauenhk. **11**, 1033 (1951).
[51] *Kaufmann, C., & Westphal, U.:* Klin. Wschr. **24/25**. 910 (1947).

### c) 17-Ketosteroids in Urine

The measurement of 17-ketosteroids in urine includes the estimation of numerous metabolites stemming from different sources[52]. *Zimmerman's* method, or one of its numerous modifications [53, 54], is the one most commonly employed in modern practice. By fractionation, the 17-ketosteroids can be subdivided into a number of derivatives[55]:

| | |
|---|---|
| Androstene-17-one | I |
| Androstanolone | II |
| Dehydro-iso-androsterone | III |
| Androsterone | IV |
| Aetiocholanolone | V |
| Androstane-17-one | VI |
| Epi-aetiocholanolone | VII |
| Unidentified products | VIII |

According to *Dingemanse*[52] fractions IV and V probably come from the ovaries.

17-ketosteroids are excreted throughout life. The amounts found are 2 to 5 mg. during childhood, 5—10 mg. during puberty and 10—15 mg. during sexual maturity. During pregnancy, the excretion of 17-ketosteroids is only slightly raised. After the menopause a slight fall in the amount excreted (5 to 10 mg.) can be observed.

The excretion of 17-ketosteroids can be influenced by physical work, also by illness and operations. In addition, considerable diurnal variations occur in healthy subjects, with maximum values during the early part of a day. Provided that a patient's mental and physical state remain relatively constant, the 24-hour excretion of 17-ketosteroids does not show much variation. This is not the case, however, in mentally disturbed patients[56] who show a wide scatter of values.

Increased 17-ketosteroid excretion may occur in patients with the adreno-genital syndrome because of adrenal hypertrophy. The same increase may be found in patients with hormone-producing tumours (pages 131, 133).

*Does the estimation of 17-ketosteroids have any diagnostic value?*

Measurements which do not distinguish between androgens (or their metabolites)

[52] *Dingemanse, E., & al.:* Acta endocr. **7**, 71 (1951).
[53] *Zimmermann, W.:* Chemische Bestimmungsmethoden, Berlin 1955.
[54] *Langecker, H.:* Biochem. Zschr. **325**, 16 (1953).
[55] *Dingemanse, E.:* J. Clin. Endocr. **12**, 66 (1952).
[56] *Reiss, M.:* 5. Symposion der Deutschen Gesellschaft für Endokrinologie, Springer-Verlag 1958.

produced by the adrenal and by the ovaries and which also include cortisol breakdown products are of only limited value. They have largely been replaced by the measurement of different corticoids (page 68). 17-ketosteroid estimations may however be of value in the diagnosis of the adreno-genital syndrome. In addition, they provide some information about the function of the adrenal and the body's potential reaction to the stress of illness or operation.
In addition, the androgen produced by the ovary can be measured if, during the period of the urine collection for 17-ketosteroid estimation, adrenal function is suppressed by dexamethasone (page 83).

### d) Gonadotrophic Hormones

The excretion of gonadotrophic hormones by the anterior pituitary can be measured in the serum or urine. Because of the small amount present in urine, 24 or 48 hour collections have to be made, and specific methods of concentration and extraction (page 56) must also be employed. So far, it is only possible to determine the total gonadotrophin excretion by use of the mouse uterine weight test[57–60] or to measure, quantitatively, the excretion of ICSH by use of the ventral prostate test[61]. The amount of FSH can be deduced from the difference between total gonadotrophins and ICSH. It is possible, but not clinically practicable, to measure the LTH (Prolactin) in serum by using the pigeon's crop test[62].
ICSH may not only be measured biologically but also by immunological methods[62a]. These methods are based on the assumption that ICSH and HCG have the same immunological properties.

Table 9. *24 Hour Excretion of total Gonadotrophins*

| | Units |
|---|---|
| Children | 2— 5 |
| Sexually mature women | |
| At the onset of menstruation | 5— 10 |
| At mid-cycle | 20— 50 |
| Climacteric and ovariectomized women | 50—200 |
| Women with hypophyseal (hypogonadotrophic) amenorrhoea | < 5 |
| Women with ovarian (hypergonadotrophic) amenorrhoea | 50—200 |

*Does the estimation of gonadotrophins have any diagnostic value?*

It is of considerable use in cases of long-standing amenorrhoea. The prognosis depends on the gonadotrophin excretion. If it is excessive, the diagnosis is ovarian failure which is not reversible. In order to make this diagnosis, the estimation of total gonadotrophins is quite sufficient.

### e) Human Chorionic Gonadotrophin in Serum or Urine

Of the many methods in existence for the measurement of chorionic gonadotrophins produced by the placenta[63], the frog test and the immunological tests have already been described (page 56). The latter also lend themselves to the quantitative estimation of HCG.
Of the other methods, which are summarized in table 10, the *Aschheim-Zondek* Reaction is of particular interest[64]. It was the first method used, and by employing serial dilutions of urine, it can provide a quantitative estimation of HCG.

*Details of the AZ test:* the subcutaneous injection of pregnancy urine into the dorsal skin of immature female mice causes characteristic changes in their ovaries. These can be observed by sacrificing the test animal 100 hours after injection:

| | |
|---|---|
| 1. Follicular ripening | Reaction I |
| 2. The appearance of haemorrhagic areas in the ovary | Reaction II |
| 3. The formation of corpora lutea | Reaction III |

[57] *Klinefelter, H. F., & al.:* J. Clin. Endocr. **3**, 529 (1943).
[58] *Lauritzen:* Med. Klin. **58**, 822 & 863 (1963).
[59] *Loraine, J.:* J. Endocr. **6**, 319 (1950).
[60] *Loraine, J., & Brown, J. B.:* J. Clin. Endocr. **16**, 1180 (1956).
[61] *Greep, R. O., van Dyke, H. B., & Chow, B. F.:* Proc. Soc. Exper. Biol. Med. **46**, 644 (1941).
[62] *Riddle, O., & al.:* Am. J. Physiol. **105**, 191 (1933).
[62a] *Wide, L.:* Acta endocr. **70**, 41 (1962).
[63] *Diczfalusy, E., & Heinrichs, H. D.:* Arch. Gynäk. **187**, 556 (1956).
[64] *Aschheim, S., & Zondek, B.:* Klin. Wschr. **7**, 1404 (1928).

Table 10. *The sensitivity of various tests for HCG.*
(*Hohlweg, W.:* Beiträge zur Fertilität u. Sterilität, Enke-Verlag 1960, p. 46, and Wien. med. Wschr. **113**, 687 [1963])

| Name of Test | Animal used | Hours | Sensitivity in I. Units | Advantages and disadvantages |
|---|---|---|---|---|
| 1. Aschheim-Zondek-Test (AZ-Test) | Immature ♀ mouse aged 3 weeks, weighing 6—9 g. | 96—120 | 3—4 | High death rate among test animals, moderate sensitivity, takes long |
| 2. Rat vaginal smear test | Immature ♀ rat aged 4—5 weeks, weighing 30—40 g. | 96 | 0,7 | Very sensitive and exact but takes long |
| 3. Ovarian hyperaemia test | ♀ mouse or rat aged 5—6 weeks, weighing 40—50 g. | $2^1/_2$—3 | 0,5 | Very sensitive and rapid, rather difficult to read |
| 4. Friedmann-Test | Young, isolated ♀ rabbit | 24—48 | 15—20 | More difficult and expensive but quicker than 1 and 2 |
| 5. Hogben or Frog-Test | South African ♀ frog (Xenop. Laevis) | 24 | 10—100 | Animals reared in captivity useless |
| 6. Galli-Mainini-Toad test | ♂ Toads of various species. | 2 | 5—20 | Rapid and cheap, too insensitive |
| 7. Pregnosticon-Test | — | 2 | 0,075—0,1 | Rapid and simple, reagents deteriorate after a time |
| 8. Ortho-Test | — | 3 | 0,3 | ditto |

Reaction I occurs if the urine contains an excessive amount of gonadotrophic hormone from the anterior pituitary (as in menopausal patients) or in circumstances where small amounts of HCG are present. Reaction III, on the other hand, implies a high urinary content of HCG.

Vaginal smear tests[65–67] are more sensitive when they are carried out in the following way: filtered urine in doses of 0.2 ml., twice daily on the first day and 0.2 ml. three times daily on the second day, are injected into immature female rats. After 50, 72 and 90 hours, vaginal smears are taken in order to determine whether oestrus has commenced.

While urinary oestrogens already give a positive reaction after 50 hours, no effect is seen with HCG unless at least 72 hours have elapsed. Generally speaking, urinary oestrogens do not interfere with this test. It is also much more sensitive than the frog test.

*Which methods are most suitable for quantitative estimations of HCG (e.g. for cases of chorion-epithelioma, page 115)?*

The AZ reaction, the vaginal smear test in rats and the immunological pregnancy test.

*Which tests are suitable in cases of extra-uterine pregnancy?*

Immunological methods are best here. They are sensitive and give rapid results. The frog test is not suitable because of frequent, false negatives.

[65] *Hohlweg, W.:* Klin. Wschr. **23**, 45 (1944).
[66] *Loraine, J.:* J. Endocr. **6**, 319 (1950).
[67] *Schneider, W., & Spurny, J.:* Geburtsh. u. Frauenhk. **15**, 921 (1955).

## f) Corticosteroids in Urine

The adrenal hormones in urine can be measured by several methods. Whichever method is used, only some of the many metabolites are measured (table 11 and table 12). The oestrogens, androgens and progestogens of adrenal origin can be measured by the tests already described. The proportions produced by the gonads must, however, be taken into account.

*Is the measurement of corticosteroids of any diagnostic value?*

The determination of excretory products in urine provides invaluable evidence with which to assess adrenal function. It is of considerable importance in the diagnosis and prognosis of adrenal disorders such as *Cushing's* Syndrome, *Addison's* disease and in the adreno-genital syndrome.

Table 11. *The detection of adrenal hormones and their breakdown products in urine*
(From *Labhardt, A.:* Klinik der inneren Sekretion, Berlin 1957, S. 278)

| | | "11-oxy-steroids or corticosteroids" | | | |
|---|---|---|---|---|---|
| | Urinary Steroids | 17-Hydroxy-corticosteroids | Formaldehy-dogenic Steroids | 17-ketogenic Steroids | 17-Keto-steroids |
| | Reaction | Porter-Silber | Corcoran and Page | Norymbersky | Zimmermann |
| | Reacting chemical group | $^{21}CH_2OH$ / $^{20}CO$ / $^{17}$ ···· OH | $CH_2OH$ / CO | $CH_2OH$ / CO / OH | O |
| Naturally occurring hormone | Metabolites | | | | |
| Cortisol ↓ ↑ Cortisone | urinary cortisol<br>urinary cortisone | + | + | + | |
| | 11-Hydroxy-aetianolone<br>11-Ketoactianolone | | | | (+) |
| Corticosterone | | — | + | — | — |
| Aldosterone | | — | + | ? | — |
| 11-Hydroxy-Androstenedione<br>Androstenedione | | — | — | — | + |

Table 12. *The detection of adrenal hormones and their breakdown products. (Oertel, W.: Personal communication)*

| Naturally occurring hormone | Metabolite in Urine | UV-Absorption 240 mμ | 17-Hydroxy-corticoster. | Formalde-hydogenic CS | Reducing CS | Ketogenic CS | 17-Ketoster. |
|---|---|---|---|---|---|---|---|
| | | | Porter-Silber | Corcoran and Page | | Norym-bersky | Zimmer-mann |
| Cortisol ↓↑ Cortisone | Cortisol, Cortisone | + | + | + | + | + | |
| | 20α-Dihydrocortisol, 20β-Dihydrocortisol | + | | + | | + | |
| | 20β-Dihydrocortisone | + | | + | | + | |
| | 5α-Dihydrocortisol, 5β-Dihydrocortisol | | + | + | + | + | |
| | 5β-Dihydrocortisone | | + | + | + | + | |
| | 5α-Tetrahydrocortisol, 5β-Tetrahydrocortisol | | + | + | + | + | |
| | 5α-Tetrahydrocortisone, 5β-Tetrahydrocortisone | | + | + | + | + | |
| | Cortol, β-Cortol, allo-Cortol, β-allo-Cortol | | | + | | + | |
| | Cortolone, β-Cortolone, allo-Cortolone, β-allo-Cortolone | | | + | | + | |
| | 6β-Hydroxycortisol | + | + | + | + | + | |
| | IIβ-Hydroxyandrosterone | | | | | | + |
| | IIβ-Hydroxyaetianolone | | | | | | + |
| | II-Keto-aetianolone | | | | | | + |
| Corticosterone ↓↑ II-Dehydro-corticosterone | Corticosterone, II-Dehydrocorticosterone | + | | + | + | | |
| | 20α-Dihydrocorticosterone, 20β-Dihydrocorticosterone | + | | + | | | |
| | 20β-Dihydro-II-Dehydro-corticosterone | + | | + | | | |
| | 5α-Tetrahydrocorti-costerone, 5β-Tetrahydrocorti-costerone | | | + | + | | |
| | 5α-Tetrahydro-II-dehydrocone, 5β-Tetrahydro-II-dehydrocone | | | + | + | | |
| Aldosterone ↓↑ II-Dehydro-aldosterone | Aldosterone, II-Dehydroaldosterone | + | | + | + | | |
| | 5α-Tetrahydroaldosterone, 5β-Tetrahydroaldosterone | | | + | + | | |
| Androstenedione ↓↑ Testosterone | Testosterone, Androstenedione | + | | | | | —, + |
| | Androsterone, Aetianolone | | | | | | + |

# J. Pubertal Disturbances and their Treatment

## I. Precocious Puberty

Precocious puberty is defined as the onset of sexual maturation before the age of 8 years. True precocious puberty is due to early activation of the ovaries by the premature onset of increased anterior pituitary function. Adrenal tumours, and tumours in the ovaries or hypothalamic-anterior pituitary system may also lead to the precocious onset of sexual maturation. One then speaks about pseudo-precocious puberty (table 13).

Precocious puberty may not only be manifested in secondary sex characteristics but also in alterations of general body build. In addition to early development of pubic hair and the early appearance of secondary sex characteristics, there is an alteration in the rate of bony development. Premature fusion of the bony epiphyses leads to the early cessation of bone growth. The "bone age" is consequently much advanced. Thus a paradoxical situation develops in which a girl with precocious puberty is at first too tall and ultimately somewhat stunted. Mental development does not keep pace with physical maturation. As with cases of delayed sexual maturation, neuroses tend to develop as a result of the disparity between mental and physical age[1].

The administration of oestrogens or chorionic gonadotrophins over longer periods causes the very somatic and genital tract changes which are associated with precocious puberty. This fact can be turned to advantage in patients with delayed puberty.

The treatment of precocity must depend on its cause. Neoplasms of the adrenal, hypothalamus, anterior pituitary and gonads must first be excluded. In cases where precocious puberty occurs without demonstrable organic cause, long-term therapy with progestogens may be of use.

**Suggested method of treatment:**

One tablet of Primolut N 5 mgs. daily for six months or longer.

## II. Delayed Puberty

If sexual development, as evidenced by the appearance of secondary sex characteristics, has not occurred by the age of 14 years, delayed puberty is a possible diagnosis. Truly delayed

[1] *Kretschmer, W.:* Neurose als Reifungsproblem, Stuttgart 1952.

Table 13. *Endocrine status with precocious puberty*
(*Prader, A.* from *Labhart, A.*: Klinik der inneren Sekretion, Berlin 1957, S. 53)

| o not detectable<br>+ present<br>+ + present in raised amounts | Metabolites in urine | | | Breasts, menses, uterine and vaginal development | Ovulation | Pubic hair |
|---|---|---|---|---|---|---|
| | Gonadotrophic hormones | 17-Ketosteroids | oestrogens | | | |
| True hypothalamic precocious puberty | | | | | | |
| 1. Idiopathic or constitutional<br>2. Organic brain disorder<br>3. Fibrous dysplasia of bone | o/+ | + + | + + | + | o/+ | + |
| Apparent precocious puberty | | | | | | |
| 1. Gonadotrophin producing tumours | + + + | + + | + + | + | o/+ | + |
| 2. Sex hormone producing tumours or hyperplasia | | | | | | |
| a) of the adrenal cortex (adreno-genital syndrome) | o | + + + | + + + | o | o | + |
| b) of the ovaries (granulosa cell and other tumours) | o | + + | + + | + | o | + |
| 3. Exogenous hormones<br>Oestrogens | o | +/+ + | + + | + | o | o/+ |

puberty is the result of retarded gonadal function due to diminished activity in the hypothalamic-anterior pituitary axis. This anomaly often rights itself and must therefore be distinguished from those disorders which come under the main heading of "apparently delayed puberty". In this respect, the following disorders are of particular importance:

### a) Ovarian Agenesis or Dysgenesis

Complete ovarian failure, as in cases of *Turner's* syndrome[2], is very rare. More usually, gonadal remnants are found containing no germ cells, only ovarian stroma[3]. The following signs are characteristic of this condition[4].

Dwarfism, barrel chest, cubitus valgus, neck webbing, genital tract hypoplasia, absence of breast development, absent or scanty pubic hair, an increased output of gonadotrophins and mental retardation.

In cases of ovarian agenesis, blood must be taken for chromosome analysis[5, 6] (page 60). In these circumstances, a male sex chromosome constitution is more common than a female one (page 87). From the twelfth year of life onwards, the signs described are very marked and easy to recognize.

Treatment (page 88) consists of substitution therapy with ovarian hormones. Genital tract development can be provoked by such measures. With cyclical drug administration, endometrial bleeding may occur as with cases of primary amenorrhoea. General skeletal growth may also be stimulated. Oestrogens may also cause the growth of pubic hair. Long term hormone therapy may also prevent osteoporosis, and may bring about improvement in mental performance[7].

Suggestion for treatment: see amenorrhoea (page 87).

### b) Dwarfism

Dwarfism is most commonly constitutional. During puberty, this type of disorder may be recognised by the presence of normal mental development and a family history of retarded physical growth. The following endocrine causes of dwarfism should be mentioned:

Dwarfism with hypothyroidism,
Dwarfism with anterior pituitary insufficiency,
Dwarfism with anterior pituitary tumours,
Dwarfism in cases of adrenal insufficiency,
Dwarfism in cases of ovarian insufficiency.

[2] *Turner, H. H.*: Endocrinology **23**, 566 (1938).
[3] *Philipp, E., et al.*: Dtsch. med. Wschr. **80**, 1721 (1955).
[4] *Prader, A.*: Schweiz. med. Wschr. **87**, 278 (1957).
[5] *Barr, M. L., & Bertram, E. C.*: Nature **163**, 676 (1949).
[6] *Tolksdorf, M., et al.*: Ärztl. Wschr. **10**, 1029 (1955).
[7] *Ebrengut, W.*: Zschr. Kinderhk. **75**, 224 (1954).

Treatment[8] depends on the underlying cause. Treatment with testosterone, thyroid hormone[9], and chorionic gonadotrophin[10] may be recommended.

It is difficult to obtain growth hormone from human pituitaries. Animal extracts have no effect. It is often difficult to decide if and when hormone therapy should commence. It is particularly difficult to predict whether growth retardation is transient[11]. For these reasons, radiographic skeletal studies are of importance. After the age of 20 years, epiphyseal fusion has occurred and therefore any form of treatment is pointless.

**Treatment:**

While testosterone preparations[9] and anabolic steroids stimulate growth, they also hasten bony maturation so that early epiphyseal fusion and cessation of growth may occur. For these reasons, treatment with these hormones is often inadvisable. Although treatment with growth hormones (STH) is more logical, the difficulty of obtaining this substance makes it impossible.

### c) Pubertal Obesity

Pubertal obesity is often a manifestation of an unsettled background[12]. The tendency often disappears after the onset of sexual maturity. In other people, obesity remains a dominant characteristic. Investigations of hormone metabolism and steroid excretion[13] have not revealed any significant deviations from normal. In many instances, juvenile obesity is due to over-eating occasioned by psychological imbalance. Diet and psychotherapy are indicated. Treatment with hormones confers no benefit. Dystrophia adiposo-genitalis, or *Frölich's* Syndrome, and also the *Laurence-Moon-Biedl*-Syndrome are differential diagnoses which have to be entertained only rarely.

## III. Abnormalities of Menstruation in Puberty

### a) Delayed Menarche

A late menarche occurs quite frequently. In the presence of normal mental and physical development it is not reasonable to entertain diagnoses such as primary amenorrhoea or delayed puberty. Constitutional, hereditary and racial factors are of considerable importance in determining the age of menarche. Hormone therapy is only indicated if menstruation has not started by the age of 18 (page 75).

### b) Abnormal Menstrual Rhythm

Treatment is not often indicated in cases where menstruation occurs too frequently or too infrequently (polymenorrhoea or oligomenorrhoea). These disturbances often indicate anovulatory bleeding due to partially developed ovarian function. Under normal circumstances, monophasic menstrual cycles are of limited duration during puberty (for treatment see page 91).

### c) Hypermenorrhoea, Polymenorrhoea

(page 95)

In the young, heavy bleeding is usually also prolonged. It is due to an incompletely developed cycle with deficient progesterone secretion. In addition, immature uterine muscle lacks contractility and this makes an extra reason for heavy blood loss. Sometimes bleeding is due to an extra-genital defect, e.g. an abnormal coagulation mechanism *(Glanzmann-Willebrand-Jürgens)*[14, 15].

**Treatment:**

One tablet Primolut N, 2—3 times daily for 16 to 18 days from the estimated eighth to tenth days of a cycle. Repeated courses of treatment subsequently, using smaller doses (figure 39).

### d) Pubertal Menorrhagia

Pubertal menorrhagia is a term which describes episodes of menorrhagia with long intervals between spells of bleeding. It is assumed that in these cases, as in those with dysfunctional bleeding in the climacteric, there is a failure of ovulation with persistence of the Graafian follicle and continuous oestrogen secretion. This results in cystic glandular hyperplasia. When the oestrogen levels fall as a result of follicular degeneration, prolonged bleeding occurs without associated shedding of the endometrium.

As with polymenorrhoea and hypermenorrhoea (page 95), an extra-genital factor may be of aetiological importance in pubertal

[8] *Prader, A.:* Schweiz. med. Wschr. **84**, 375 (1954).
[9] *Escamilla, R. F.:* J. Clin. Endocr. **14**, 255 (1954).
[10] *Lederer, J.:* Ann. endocr. **13**, 207 (1952).
[11] *Bierich, J. R.:* Medizinische **1957**, 1375.
[12] *Weißbecker, L.:* Dtsch. med. Wschr. **80**, 263 (1955).
[13] *Ströder, J., & Zeisel, H.:* Zschr. Kinderhk. **75**, 683 (1955).
[14] *Elert, R.:* Schweiz. med. Wschr. **76**, 1090 (1946).
[15] *Geipel, K., & Löbr, G.-W.:* Med. Welt **1963**, 2678.

menorrhagia[14,15]. The prognosis in cases of pubertal menorrhagia is good. At the age of about 20, the menstrual cycle usually becomes regular. Some investigators, however, have noted that sexually mature women with a history of pubertal menorrhagia often have menstrual disturbances and are frequently infertile[17].

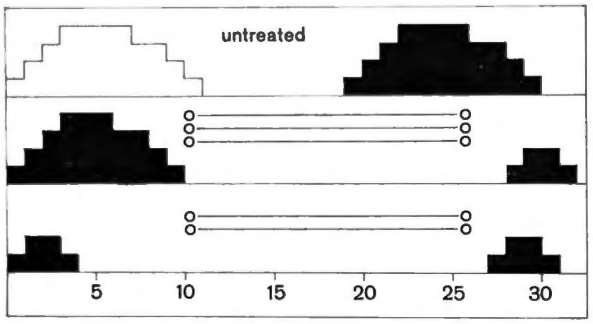



Figure 39. Scheme of treatment for cases of polyhypermenorrhoea. 1 tablet of Primolut N 3 times daily. Further treatment consists of 1 tablet of Primolut N twice daily in the next interval between periods.

**Treatment:**

The availability of nortestosterone derivatives (progestational substances) markedly brightens the outlook for these cases. Repeated curettage, ligation of the uterine artery, sub-total or total hysterectomy and irradiation of the spleen need no longer be considered. Treatment depends on general findings and results of blood analysis. In the presence of marked anaemia, treatment with ethinyl-nortestosterone acetate for several weeks or months is indicated[18,19] and leads to an arrest of haemorrhage during which recovery can occur. In other cases, cyclical treatment with hormones is preferable.

**Suggestions for treatment:**

I. With anaemia, two tablets of Primolut N daily for 3—5 weeks until the anaemia is corrected. Then continue as in paragraph III.

II. With persistent bleeding, three tablets of Primolut N daily, for 10 days. After a subsequent withdrawal bleeding, continue as in paragraph III.

III. One dragee of Anovlar 21 from the fifth to the twenty-fifth days of three menstrual cycles. This treatment should be repeated if subsequent spontaneous cycles still show a monophasic basal temperature pattern.

## IV. Gigantism

Apart from pathological growth which may occur in cases of acromegaly, puberty is frequently a time of unusually rapid growth due to hereditary and constitutional influences. Epiphyseal closure may be hastened by oestrogens which can be used to curb an excessive growth tendency. Clinical experience has shown that menstrual disturbances do not occur subsequently[20,21].

**Treatment[22]:**

Cyclic administration of Progynon Depot (Primogyn Depot) 10 mgs. on the 1st, 4th and 10th days of a cycle.
Proluton Depot (Primolut Depot) 250 mg. on the 10th day of a cycle. Progynon Depot 10 mg. on the 5th, 9th and 16th days and Proluton Depot 250 mg. on the 16th day of the next twelve menstrual cycles. It may be necessary to continue treatment longer and until there is evidence of epiphyseal closure.

[16] *Napp, J. H., & Protzen, H.:* Dtsch. med. Wschr. **85**, 1007 (1960).
[17] *Fries, K.:* Geburtsh. u. Frauenhk. **22**, 511 (1962).
[18] *Ufer, J.:* Münch. med. Wschr. **103**, 1982 (1961).
[19] *Ross, R. A.:* Amer. J. Obstetr. Gynec. **86**, 77 (1963).
[20] *Goldzieher, M. A.:* J. Clin. Endocr. **16**, 249 (1956).
[21] *Freed, S. Ch.:* J. Amer. Med. Ass. **166**, 1322 (1958).
[22] *Whitelaw, M. J., & Foster, Th. N.:* J. Pediatr. **61**, 566 (1962).

# K. Treatment of Gynaecological Disorders in Sexually Mature Women

## I. Disturbances of Menstruation

### a) Classification

The following disorders can be recognized: amenorrhoea, menstruation of abnormal rhythm, abnormal bleeding with a regular cycle and dysfunctional bleeding with cystic glandular hyperplasia. A method of classification according to the presence or absence of ovulation may be quite useful:

- Primary amenorrhoea, Secondary amenorrhoea — No Graafian follicles — Failure of ovulation
- Dysfunctional bleeding with cystic glandular hyperplasia; Anovulatory menstrual cycles — Ripening follicles present — Failure of ovulation
- Abnormal menstrual rhythm: Oligomenorrhoea, Polymenorrhoea; Abnormal bleeding with a regular cycle: Ovulatory bleeding, Premenstrual bleeding, Postmenstrual bleeding, Hypermenorrhoea, Hypomenorrhoea; Dysmenorrhoea; Premenstrual tension syndrome — Ovulation occurs

The many types of menstrual disturbance may at first seem confusing, particularly as symptom combinations tend to occur (e.g. Hyperpolymenorrhoea). The question is how it is possible in general practice to make an accurate diagnosis without resorting to more complicated laboratory tests. A careful history and gynaecological examination usually suffice. The question of whether or not ovulation is occurring is usually answered by studying a carefully kept basal body temperature record. The appearance of the cervix and repeated examination of cervical mucus for "Spinnbarkeit" and "Ferning" (page 55) also provide useful information.

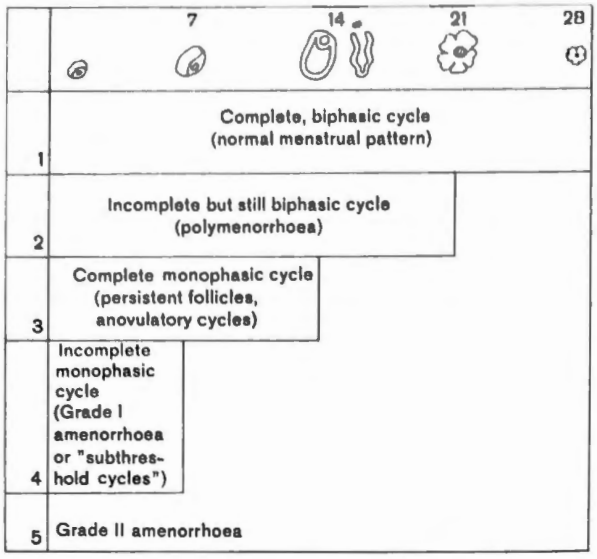



Figure 40. Scheme showing various types of ovarian insufficiency. The vertical lines indicate the point in the cycle at which ovarian function is arrested. (*Tietze, K.* in Seitz-Amreich: „Biologie und Pathologie des Weibes", Berlin-Wien II, 2, 614 [1952])

Endometrial biopsy or diagnostic curettage are measures which may confer therapeutic benefit. Therapeutic tests using hormone injections may also be of value. All other procedures demand specialist knowledge or technique and are not usually necessary in outpatients.

### b) Hormones to Control or Stimulate Bleeding

By using oestrogens, progestogens and androgens, uterine bleeding can be provoked just as easily as it can be controlled. This apparent contradiction can be explained in the following way.

1. Oestrogens (page 20) cause proliferative changes in the endometrium. If oestrogen therapy is suddenly withdrawn or continues for rather a long period of time, bleeding occurs and is described as being of the oestrogen withdrawal type. This is because oestrogen stimulation is no longer sufficient to maintain the endometrium in a state of proliferative activity. This type of bleeding can be controlled by increasing the stimulus for proliferative changes with a higher dose of oestrogens.

2. Progesterone (page 21 and page 30) can only act on endometrium showing oestrogenic proliferative activity. The withdrawal of progesterone provokes bleeding (figure 42). Menstruation is really a form of progestational withdrawal bleeding. If insufficient amounts of progesterone are given for more than one week, withdrawal type bleeding can already occur during treatment (this is known as breakthrough bleeding). On the other hand, progestogens have a good haemostatic effect. It is particularly marked with nortestosterone derivatives.

3. Androgens (page 22) may also cause bleeding if they act on proliferative endometrium. They probably have a weak progestational effect. Alternatively, by suppressing the output of gonadotrophins from the anterior pituitary and hence the endocrine function of the Graafian follicle, androgens may cause bleeding of oestrogen-withdrawal type. Androgens may, however, control bleeding by their beneficial effect on uterine contractility.

Uterine bleeding may thus arise in one of many different ways. An untimely fall of oestrogen or progesterone secretion constitutes the most important aetiological factors.

The severity and duration of bleeding will depend on the state of the endometrium (transitional, proliferative or showing the changes of cystic glandular hyperplasia).

*Question*

In what way is menstrual bleeding different from the bleeding which occurs with cystic glandular hyperplasia or after small doses of progesterone in patients with amenorrhoea?

*Answer*

In each case one is, in fact, dealing with hormone withdrawal bleeding.

Normal menstruation is bleeding from endometrium which has undergone secretory changes. These are the result of follicular rupture and corpus luteum formation. Bleeding occurs as soon as the corpus luteum fails to produce a sufficient amount of progesterone and oestrogen. The endometrium is rapidly shed down to its basal layer.

The dysfunctional bleeding of cystic glandular hyperplasia occurs when relatively insufficient amounts of oestrogen are unable to support an endometrium with pathological proliferative changes. No progesterone is being formed and the endometrium has not undergone secretory changes. Bleeding occurs from the surface of the endometrium without associated shedding. After a matter of several weeks, necrosis of the endometrium occurs and it is subsequently expelled.

In women with secondary amenorrhoea of short duration, the endometrium is proliferative as a result of continuous oestrogen

Figure 41. Schematic representation of withdrawal bleeding in an ovariectomised woman receiving 1 mg. of oestradiol benzoate on days marked ▼.

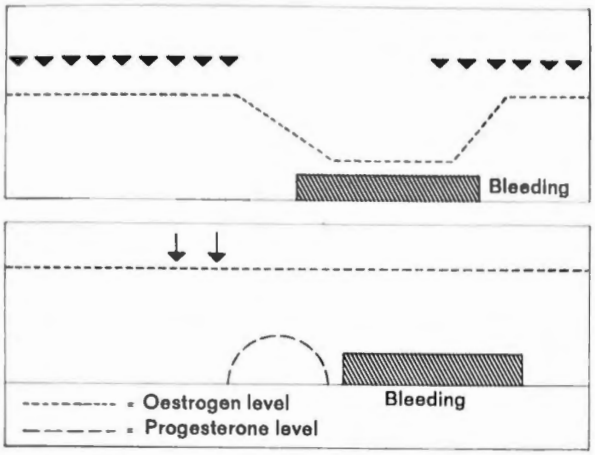



Figure 42. Diagram to show bleeding with progesterone 20 mg. on 2 consecutive days (↓) in a patient with secondary amenorrhoea. The endometrium is proliferative due to persistently elevated oestrogen levels.

secretion from a partially ripened follicle which does not go on to maturity. The formation of progesterone does not occur. 20—40 mg. of progesterone in fact do not cause secretory transformation of proliferative endometrium. However, the bleeding which occurs several days after the discontinuation of gestagen therapy is of the "superficial" type and is not accompanied by normal menstrual shedding of the endometrium.

### c) Amenorrhoea

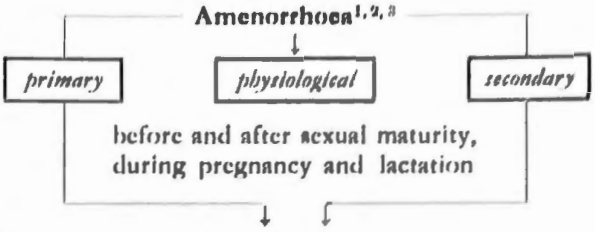
Amenorrhoea is defined as the absence of menstruation during the years of sexual maturity. In a way, menstrual bleeding can be considered the result of non-fertilization of an ovum (page 30). Its absence therefore may be due to a number of causes. Generally speaking, it is useful to distinguish between physiological and pathological amenorrhoea. If the first type of amenorrhoea can be excluded, considerable experience and knowledge is required to pinpoint the exact cause.

The following remarks will demonstrate the many possible causes of amenorrhoea. It is not sufficient to distinguish between primary and secondary amenorrhoea, however significant this subdivision may be. In the classification given, nine main causes of amenor-

[1] *Finkbeiner, H.:* Therap.woche 7, 89 (1956/57).
[2] *Husslein, H.:* Wien. med. Wschr. 104, 109 (1954).
[3] *Staemmler, H. J.:* Gestörte Regelung der Ovarialfunktion, Springer-Verlag 1964.

### 1. Types of Amenorrhoea

Table 14




| | |
|---|---|
| I. General Causes | Infantilism<br>Delayed puberty<br>Pluriglandular insufficiency<br>Severe systemic disease<br>Toxic states<br>Nutritional deficiency (e. g. vitamins)<br>Stress at work |
| II. Vaginal Causes | Complete or partial absence of the vagina<br>Hymenal atresia* |
| III. Uterine causes | Absent uterus*<br>Uterine malformation<br>Uterine hypoplasia<br>Atresia of the cervix<br>Atresia of the uterine cavity<br>Destruction of endometrium by: curettage, cautery, infection |
| IV. Ovarian causes | Ovarian agenesis*<br>Rudimentary ovaries<br>Early ovarian failure (premature climacteric)<br>Polycystic ovary (Stein-Leventhal syndrome)<br>Ovarian insufficiency due to irradiation or hormone therapy<br>Persistent Graafian follicles<br>Ovarian tumours |
| V. Hypophyseal causes | Insufficiency due to underdevelopment (?)<br>Secondary pituitary failure due to tumours<br>— trauma<br>— after delivery (Sheehan's syndrome) |
| VI. Hypothalamic causes | Primary hypothalamic insufficiency (?)<br>Secondary failure of the hypothalamus due to tumours<br>— trauma<br>— unknown reasons<br>Dystrophia adiposogenitalis<br>Dietary obesity<br>Anorexia nervosa |

*Only found in cases of primary amenorrhoea.

| | |
|---|---|
| VII. Cerebral causes | Psychological trauma (Flight/fright amenorrhoea)<br>Psychosis |
| VIII. Adrenal causes | Adreno-genital syndrome due to adrenal dysfunction<br>— adrenal tumours<br>Cushing's syndrome |
| IX. Thyroid Disorders | Hyperthyroidism<br>Myxoedema |

rhoea are presented. They are not all of endocrine origin. Thus, vaginal and uterine amenorrhoea are due to mechanical causes. They are, however, relatively infrequent. It is thought that about 70% of all cases of amenorrhoea are of hypothalamic origin. This includes those cases where the original disturbance occurred in a higher brain centre. About 20% of cases are due to primary failure of the ovaries. In these cases it is vital to know whether this failure is "central or peripheral" in origin. It is not known how frequently amenorrhoea is due to disorder of the anterior pituitary. True Sheehan's-syndrome is very unusual.

In considering this classification, it should be remembered that it is not possible to cover all combinations. Thus, delayed puberty may be due to disorder of the anterior pituitary or hypothalamus. As follicular maturation and ovulation are under the control of gonadotrophic hormones, it is most likely that cystic follicles reflect a central disorder rather than one of ovarian origin.

As amenorrhoea can be classified according to aetiological factors and also in other ways, it is necessary to present a second method of subdividing these cases. This does not contradict the classification already presented.

### A further scheme for classifying cases of amenorrhoea

Table 15

| | |
|---|---|
| Primary Amenorrhoea | Menstruation has never occurred although the patient is already 18 years of age. |
| Secondary Amenorrhoea | Absence of menses in a patient who previously had periods. |
| "Generative" Amenorrhoea | Grade I Amenorrhoea. Follicular maturation and ovulation are disturbed. |
| "Vegetative" Amenorrhoea | Grade II Amenorrhoea. A disturbance of follicular ripening is associated with deficient oestrogen production. |
| Hyperhormonal Amenorrhoea | The endometrium is hyperplastic as it has been exposed to the effect of oestrogens from the Graafian follicle for too long. |
| Hypohormonal Amenorrhoea | The endometrium shows only slight proliferative changes or frank atrophy because too little hormone is being produced by the Graafian follicle. |
| Hypergonadotrophic Amenorrhoea | The urine contains increased amounts of gonadotrophic hormone because of a negative "feedback" effect on the anterior pituitary caused by failing hormone production by the Graafian follicle. |
| Hypogonadotrophic Amenorrhoea | Almost no gonadotrophic hormones detectable in urine. There is a disturbance of the hypothalamic anterior pituitary system. |

**Example:** Stress amenorrhoea is almost always secondary and often hyperhormonal or hypogonadotrophic and the result of hypothalamic disturbance. It is usually a Grade I amenorrhoea as only the reproductive function of the ovary is disturbed.

### 2. Diagnosis and Treatment of Amenorrhoea

It is obvious that an aetiological classification of amenorrhoea presents considerable difficulties in circumstances where this disorder is not due to uterine or vaginal causes. The presenting symptoms, the history, general and gynaecological examination, simple diagnostic measures such as trial hormone injections (page 54) and vaginal cytology may all not provide sufficient information on which to base an accurate diagnosis. Complicated procedures such as assays of oestrogen, pregnanediol and gonadotrophin also do not clarify the situation. These facts are not entirely surprising if one considers the following points:

1. If the gonadotrophin test (page 55) leads to ovulation and menstruation it indicates that the ovaries are functionally intact. If, however, the test is negative one still does not know whether amenorrhoea is ovarian or hypothalamic in origin[5].

2. Tests for hypothalamic function are mainly concerned with studying the effect of the hypothalamus on general metabolism. In

[4] *Herrmann, W.:* Praxis **40**, 910 (1951).

[5] *Staemmler, H.-J.:* Klin. Wschr. **38**, 940 (1960).

view of the special connections which exist between the hypothalamus and the anterior pituitary, these tests are inadequate. Further, hypothalamic and anterior pituitary disorders may both be associated with low urinary gonadotrophin levels.

3. The quantitative estimation of gonadotrophins in urine or serum mainly measure their ICSH-component. To date FSH, the hormone responsible for follicular development, has only rarely been measured in cases of amenorrhoea. Nothing is known about the role of prolactin in cases of amenorrhoea. This hormone, present in humans, is only known to be essential to formation of the corpus luteum in rats. In spite of the gaps in knowledge, gonadotrophin assays in urine are of importance in all cases of long-standing amenorrhoea. Low levels (under 5 HMG-units) indicate amenorrhoea of central origin. Raised values (over 30 HMG-units) occur in association with ovarian failure. This finding carries a poor prognosis for the patient. In most cases, amenorrhoea is associated with a normal gonadotrophin output and in these it is not possible, with present methods of diagnosis, to distinguish separate aetiological factors.

4. Oestrogen determinations have limited value. They provide no evidence with which to assess the severity or cause of the disturbance. Low levels of oestrogen excretion combined with an excessive output of gonadotrophins confirm a diagnosis of amenorrhoea due to ovarian disorder.

5. The estimation of pregnanediol in urine is only necessary in circumstances where information is required about the presence or absence of ovulation.

## 3. Special Comments

*History*

This provides valuable information, not only about the duration of amenorrhoea but also about its cause. In cases of amenorrhoea, enquiries about family history, associated mental and physical disturbances as well as the age of menarche are particularly relevant. In cases of post-partum amenorrhoea it is important to obtain details about labour and delivery. A history of post-partum haemorrhage may not infrequently be obtained (see *Sheehan's* syndrome page 85). Primary amenorrhoea associated with mental retardation or malformation suggests an abnormal chromosome constitution. Cyclical episodes of pain suggest ovarian function with some mechanical disturbance as the underlying cause of amenorrhoea.

*General Examination*

A special search should be made for signs of general endocrine disturbance. Myxoedema, dwarfism, dystrophia adiposo-genitalis are some of the conditions important in this respect. Virilisation may occur in cases of adrenal, ovarian or constitutional abnormality. Breast development shows no correlation with the severity of a disorder. *Staemmler*[3] observed ovarian or hypothalamic amenorrhoea in normal women with fully developed breasts.

*Pelvic Examination*

Vaginal and uterine malformation must be excluded. This is important in deciding whether amenorrhoea is of mechanical or endocrine origin. The size of the uterus and ovaries must be determined during pelvic examination. A relatively well developed uterus indicates the presence of oestrogens. Enlarged ovaries suggest multiple cystic follicles (as in *Stein-Leventhal* syndrome).

The prognosis[5] in cases of amenorrhoea depends on the underlying cause and on the length of history. With primary amenorrhoea, the outlook is poor, particularly as about one-third of all cases have some demonstrable genetic disorder. Women with long-standing amenorrhoea and with atrophic genital tract changes are also very resistant to treatment. A favourable prognosis can be given in cases where menstruation has only been absent for a short time or where there is reason to believe that reversible exogenous factors are in operation. General measures (such as diet, weight reduction or balneology etc.) are not considered in detail here. If a spell of amenorrhoea cannot be broken by hormone treatment or other suitable measures, this raises the suspicion of deep, underlying disturbance (see special forms of amenorrhoea, pages 82 to 88).

## 4. Primary Amenorrhoea[6, 7]

*Definition:* If menstruation has not occurred by 18 years of age, the diagnosis is obviously primary amenorrhoea—always a serious con-

[6] *Schüller, E.:* Wien. klin. Wschr. 70, 361 (1958).
[7] *Käser, O.:* Dtsch. med. Wschr. 83, 1461 (1958).

dition! It may be due to hypothalamic, anterior pituitary, ovarian, adrenal or genital tract disturbances. The following disorders may be present in a patient who complains of "primary amenorrhoea": adreno-genital syndrome, *Stein-Leventhal* syndrome, testicular feminisation syndrome, gonadal dysgenesis (the reader is referred to each respective heading). If malformations or mental retardation is simultaneously present, a suspicion of numerical or structural aberration in the chromosome constitution arises[8]. In such cases, the problem can only be resolved by detailed examination.

*Differential diagnosis*

1. By using a progesterone test (page 54) (Proluton [Primolut] 20 mg. or one ampoule of Duogynon [Primodos, Proluton Z Fort] on two consecutive days), it is possible to exclude genital tract abnormality and to decide whether the ovaries are secreting significant amounts of oestrogen or not. If bleeding occurs within 10 days of the second injection, a rare occurrence in cases of primary amenorrhoea, it can be assumed that the endometrium is capable of functioning normally and that there is no serious underlying disturbance (Grade I amenorrhoea or generative amenorrhoea). Further treatment resembles that given to cases of secondary amenorrhoea.

2. The gonadotrophin test (page 55, PMS 1000 units × 3 and HCG 5000 IU × 3) is a relatively simple diagnostic procedure. From basal body temperature records, observations on cervical mucus and histological examination of endometrium removed by endometrial biopsy, it is possible to determine whether ovulation has occurred or not.

3. The proliferative activity observed in vaginal smears provides information about ovarian function. A type 3 or type 4 smear means that the ovaries are secreting oestrogens.

*Prognosis:* The prognosis is relatively good in cases where there are positive responses to the progesterone and gonadotrophin tests. The treatment is as with cases of secondary amenorrhoea.
In all other cases the prognosis is poor. A full picture of the disorder can be obtained by quantitative assays of gonadotrophins in urine, curettage, examination of the chromosome constitution and tests for hypothalamic function. Culdoscopy or even laparotomy are often indicated in order to obtain a clear picture of the degree of ovarian development (e.g. agenesis or hypoplasia).
Treatment often merely consists of substitution therapy with sex hormones (see suggestions for treatment page 81).

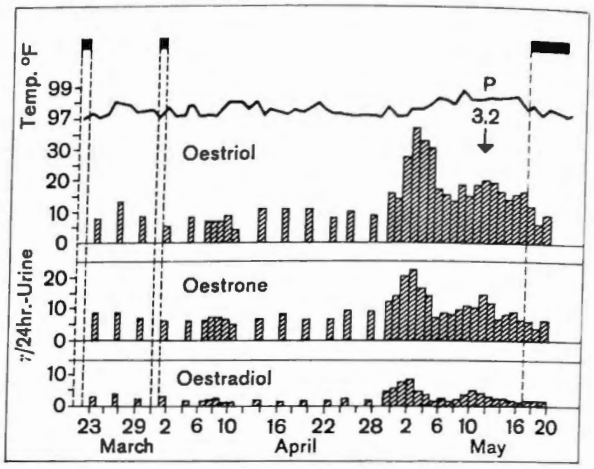



Figure 43. Oestrogen excretion in a 29-year-old patient with secondary amenorrhoea. In May, the levels rise and two peaks are seen. The pregnanediol excretion (P) is 3.2 mg./24 hours during the second peak. The blood loss ▬ starting on 17 th May represents true menstruation.
(*Brown, J. B.*, et al.: J. Obstetr. Gynaec. **66**, 177 [1959])

## 5. Secondary Amenorrhoea

The history often suggests the cause. Amenorrhoea may occur after severe illness, fright, emotional disturbance, change of climate, delivery or miscarriage.
After general examination, it may be possible to say whether amenorrhoea is due to endocrine disorder and if treatment with hormones is indicated. Severe systemic disease (e.g. tuberculosis, toxic states, malnutrition) are circumstances in which hormone therapy is contra-indicated. In these cases, menstruation often returns with an improvement in general condition.
It is particularly important to look for uterine atrophy during pelvic examination. The uterine cavity should be sounded in cases where amenorrhoea follows diagnostic curettage. In this way, endometrial atresia can be excluded.

### Long-standing secondary amenorrhoea

As in cases of primary amenorrhoea, a progesterone test (page 54) is a good first manoeuvre. A positive result implies adequate

[8] *Gropp, A., et al.:* Klin. Wschr. **41**, 345 (1963).

endocrine function of the ovary and Grade I amenorrhoea. The prognosis is good. Treatment is as with cases of secondary amenorrhoea of short duration (page 81).

With longer spells of amenorrhoea (one year or more), the test is often negative. As a result of severe ovarian insufficiency (a failure of reproductive and endocrine function) the endometrium may have become markedly atrophic and incapable of responding to progesterone without preliminary oestrogen therapy.

A negative progesterone test means that further diagnostic measures are indicated. The absence of withdrawal bleeding after two injections of progesterone 20 mg. or two ampoules of Duogynon (Primodos, Proluton Z Fort) demand that more information should be obtained. This can be done by employing an oestrogen test. If, within four weeks of an injection of 20 mg. of a depot-oestrogen (e.g. Progynon Depot [Primogyn Depot]), withdrawal bleeding has not occurred (a negative oestrogen test) a uterine cause of amenorrhoea can be assumed. By means of diagnostic curettage it must be established whether the uterine cavity is still lined by endometrium. If no endometrium is obtained, an endometrial transplant followed by oestrogen therapy should be considered[9]. If fragments of endometrium are obtained, repeated treatment using the *Kaufmann* regime (page 81) is indicated.

If the oestrogen test is positive, it is, as with cases of primary amenorrhoea, important to decide whether the disturbance is central or ovarian in origin.

Post-partum amenorrhoea, if not due to uterine abnormality is often central in origin. For further details see page 85.

Cases of long-standing secondary amenorrhoea are often due to ovarian disorder. The gonadotrophin test is negative (page 55) and the excretion of gonadotrophins in urine is excessive. The patient often gives a history of hot flushes which, as in climacteric women, are thought to be due to excessive anterior pituitary function (hypergonadotrophic). The abnormality is often due to poor ovarian development, with early exhaustion of the supply of primordial follicles (premature climacterium). Sometimes it may be due to the *Stein-Leventhal* syndrome (and large grey ovaries).

[9] *Kraatz, H.:* Zbl. Gynäk. 65, 1888 (1941).

The prognosis with these disorders is the same as for cases of primary amenorrhoea. As with primary amenorrhoea, substitution therapy with sex hormones is indicated in order to prevent premature atrophy and circulatory or metabolic disturbances.

Secondary amenorrhoea can be treated with sex hormones or with gonadotrophic hormones. Clomiphene has also been used with success.

Sex hormones often stimulate the development of a small or atrophied uterus. Their use is, therefore, particularly indicated in cases where there is evidence of uterine hypoplasia (page 97). They cause transient inhibition of the hypothalamic-anterior pituitary axis and in favourable cases, the gonadotrophin output increases after the end of medication so that ovulation results[10,11].

The use of gonadotrophins demands potential function of the hypothalamic-anterior pituitary axis and also the presence of Graafian follicles capable of being stimulated.

The following gonadotrophin preparations may be used for the treatment of amenorrhoea:

Preparations of PMS obtained from pregnant mares' serum (page 23) contain a mixture of FSH and ICSH activity. Preparations of HCG are made from human pregnancy urine (page 23) and their action resembles that of ICSH (LH) from the anterior pituitary.

HMG is prepared from menopausal urine and contains a mixture of human FSH and human ICSH.

*Animal hypophyseal extracts*[12]

*Human hypophyseal extracts*[13–15]

Depending on the method of preparation, they contain varying proportions of FSH and ICSH. As the result of evidence from numerous experiments, there are two phases to any form of treatment. A preparation rich in FSH is given first and is followed by one which contains high levels of ICSH. The optimal combination in any particular case is difficult to determine because of the limited

[10] *Hohlweg, W.:* Dtsch. Gesd.wes. 11, 245 (1956).

[11] *Buschbeck, H.:* Medizinische 1957, 1523.

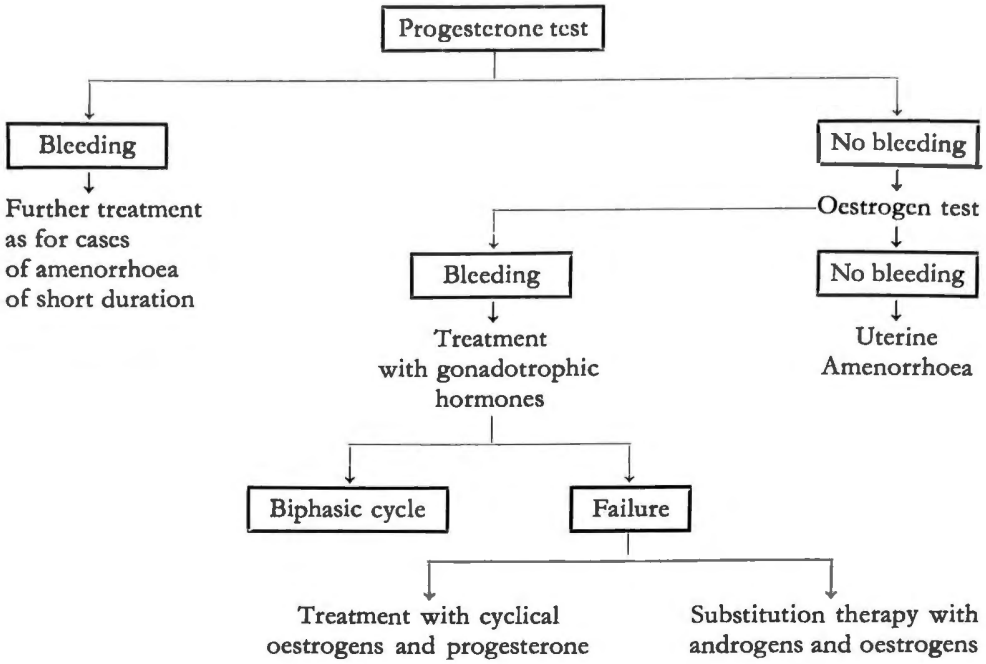
[12] *Daume, E., & Dörner, G.:* Intern. Fed. f. Gynäk. u. Geburtsh. III. Weltkongr., Wien 1961, Bd. II: 229.

[13] *Bettendorf, G.:* Ärztl. Forsch. 16, 308 (1962).

[14] *Buxton, C. L., & Herrmann, W.:* Amer. J. Obstetr. Gynec. 81, 584 (1961).

[15] *Gemzell, C. A., & Diczfalusy, E.:* J. Clin. Endocr. 18, 1333 (1958).

Table 16. *Management in cases of long-standing secondary amenorrhoea*




nature of the diagnostic tests that can be employed (page 55). For reasons of species specificity, it is likely that human FSH is more effective than FSH from animal sources. With long-term therapy in which animal extracts are used, one must reckon with a loss of effectiveness due to the formation of antihormones. In this context, it should be mentioned that antihormones seem to cause less trouble in human beings than one might expect.

The results of gonadotrophin therapy, however clearly indicated it may be, are often disappointing. The treatment scheme devised by *Staemmler* (figure 44) can only be used clinically. It depends on the assumption that PMS and FSH have the same biological activity. This concept can barely be substantiated[16] (page 43). Treatment with sex hormones is more simple. It not only results in menstrual bleeding but prevents atrophic changes. In addition, cyclical monthly therapy may have a beneficial central effect as a result of which spontaneous biphasic cycles appear again after treatment is discontinued.

Clomiphene (page 8) can also induce ovulation[17]. It is assumed that this drug affects the production of "releasing factors" (page 14) which in turn stimulate the output of gonadotrophins[18].

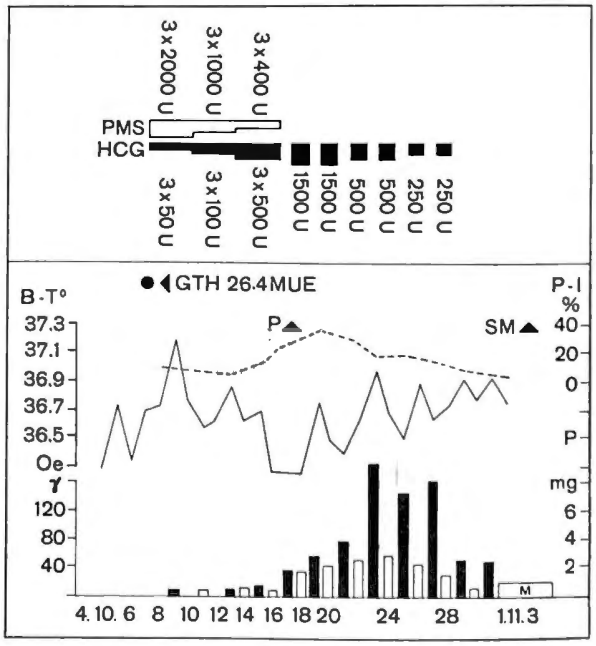



Figure 44. Treatment of secondary amenorrhoea with gonadotrophins. A combination of pregnant mares' serum (PMS) and human chorionic gonadotrophin (HCG) gives a biphasic cycle with rising urinary oestrogen (black bars) and pregnanediol (white bars) levels. GTH = gonadotrophin excretion before treatment in mouse uterine weight units (MUE). (*Staemmler, H.-J.*: Med. Klin. **55**, 1221 [1960])

[16] *Dörner, G., & Hohlweg, W.*: Klin. Wschr. **39**, 518 (1961).

[17] *Zander, J., & Buntru, G.*: Geburtsh. u. Frauenhk. **23**, 871 (1963).

[18] *Smith, O., & al.*: J. Amer. Med. Ass. **184**, 878 (1963).

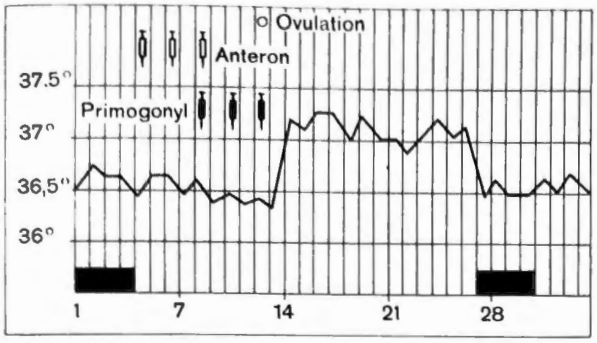



Figure 45. Waking temperature curve with secondary amenorrhoea. Ovulation followed treatment with 1,000 IU PMS and 5,000 IU HCG both × 3.

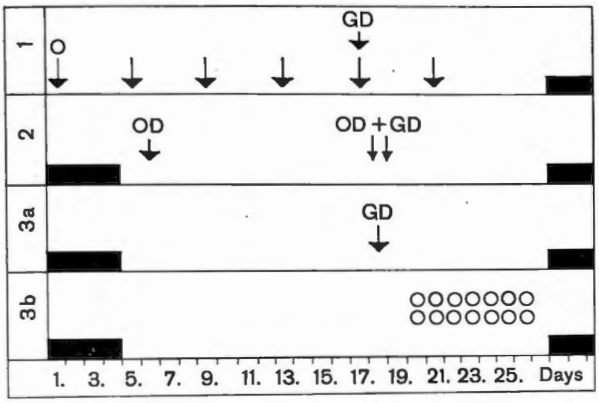



Figure 46. Treatment of a case of long-standing secondary amenorrhoea with: Oestradiol benzoate (O) and a progestogen depot (GD) [1]. Oestrogen depot (OD) and a progestogen depot (GD) [2]. Progestogen depot (GD) in 3 phases [3a]. Instead of progestogen depot, tablets of Primolut N (OOOO) were used in the next cycle [3b].

## Suggestions for Treatment

*a) Gonadotrophins*[19–21]

Anteron (Primantron) 1000 IU on alternate days x 3.

Primogonyl 5,000 IU with the last injection of Anteron and then on alternate days x 3 or 4 until the basal body temperature begins to rise indicating that ovulation has occurred.

During therapy, and particularly with repeated courses of treatment, frequent bimanual examinations are important (see *Stein-Leventhal* syndrome).

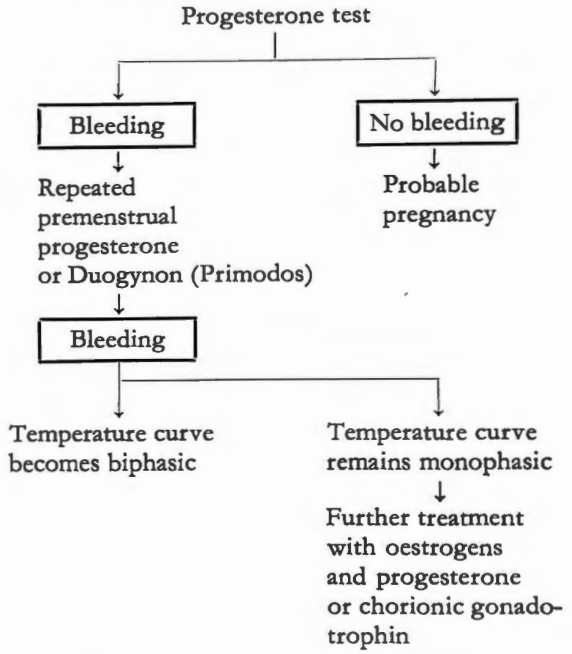
*b) Oestrogen-Gestagen Therapy* (Kaufmann's modification)

1. Six injections of oily oestradiol benzoate 5 mg. with intervals of 4 days between injections. In addition, Proluton Depot (Primolut Depot) 250 mg. on about the 18th day.

2. Continuing treatment with sex hormones after the first episode of bleeding: Progynon Depot (Primogyn Depot) 10 mg. on the 6th and 18th days of the menstrual cycle with progestogen therapy as in 1 above.

3. After several repetitions of 2, further treatment with depot progestogens alone or in combination with tablets[22]: Proluton Depot 250 mg. (Primolut Depot) on the 18th day of the cycle or 2 tablets Primolut N from the 20th to 26th days of the cycle (see 3a and 3b, figure 46).

Table 17. *Scheme of management for cases of short-term secondary amenorrhoea*




## Secondary amenorrhoea of short duration

In most cases, spontaneous menstruation starts again as soon as the causative factor of this relatively harmless condition is alleviated. An improvement in living conditions, the treatment of severe systemic disease and solution of any emotional problems there might be are of the utmost importance.

*Hormone Treatment.* It is quite often desirable to alleviate anxiety about pregnancy or organic disease by treatment which is directed at reassuring the patient with an

[19] *Rydberg, E.:* Acta obstetr. gynec. Scand. 18, 1 (1938).
[20] *Staemmler, H.-J.:* Med. Klin. **52**, 55 (1957).
[21] *Will, J.:* Med. Klin. **50**, 1859 (1955).
[22] *Holmstrom, E. G.:* Amer. J. Obstetr. Gynec. **68**, 1321 (1954).

episode of withdrawal bleeding. Two injections of progesterone 20 mg., 2 ampoules of Duogynon (Primodos, Proluton Z Fort) or 1 ampoule of Duogynon simplex, almost always lead to menstrual bleeding. Prostigmine has the same effect and can be used instead of progestogens[23]. If the basal body temperature curve remains monophasic, cyclical repetition of progesterone therapy may be advisable. If several such attempts do not lead to ovulation, a treatment like that for long-standing amenorrhoea is indicated.

### 6. Conclusions about the Treatment of Amenorrhoea

Not all types of amenorrhoea demand treatment with hormones.

Not too much time, however, should be allowed to elapse before deciding to use hormones as the chances of successful therapy diminish as the duration of amenorrhoea increases.

To date, treatment with gonadotrophic hormones did not offer very favourable prospects. Better results can be expected with more potent hypophyseal FSH preparations. In the foreseeable future, it is possible that the hypothalamic "releasing factors" may be available.

Clomiphene only seems to be effective in cases where amenorrhoea is associated with a normal output of gonadotrophins[17]. The substitution of sex hormones is indicated in cases where there is no permanent beneficial effect. This prevents the early appearance of atrophic changes in the genital tract and at other sites (osteoporosis).

## Special types of amenorrhoea due to organic causes

### 7. Amenorrhoea with Uterine Hypoplasia

(see Hypoplasia of the Genital Tract, page 97)

Inadequate uterine development is a particularly frequent finding in cases of primary amenorrhoea. The prognosis does not depend on the degree of uterine hypoplasia. Notwithstanding, any treatment with hormones which stimulates uterine development sufficiently to overcome any existent hypoplasia, would receive preference. In cases where the uterine cavity measures less than 3.5 cm. it is unlikely that treatment will render the genital tract normal[24]. In order to stimulate growth, the use of oestrogens is required. They should be given in depot form over a matter of several months. At a later date, cyclical therapy with oestrogens and progesterone can be used instead. Intra-uterine applications of oestrogens may also give successful results.

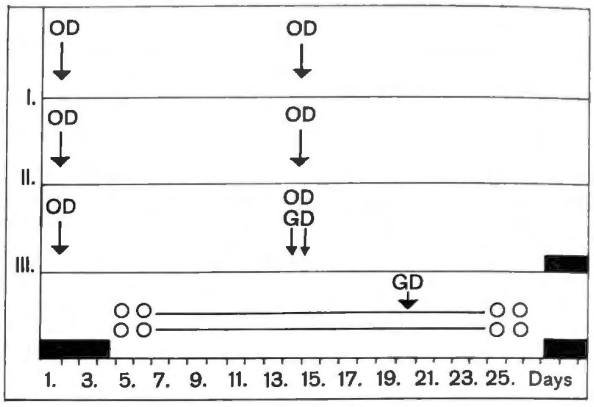



Figure 47. Three-stage treatment of a patient with amenorrhoea and marked uterine hypoplasia using oestrogen depot (OD) (Progynon Depot, Primogyn Depot), progestogen depot (GD) (Proluton Depot, Primolut Depot) and oestrogens (OO) (Progynon C tablets, Primogyn C).

**Treatment:**

Parenteral treatment with depot hormones (figure 47).

*Phase I:* Progynon Depot (Primogyn Depot) 10 mg. every 2 weeks for 2 to 3 months.

*Phase II:* Further treatment with Proluton Depot (Primolut Depot) 250 mg. combined with Progynon Depot (Primogyn Depot) 10 mg. Immediately after the withdrawal bleeding, which occurs about 10 days later, further cyclical treatment with 10 mg. Progynon Depot (Primogyn Depot) and, 14 days later, another 10 mg. Progynon Depot (Primogyn Depot) and 250 mg. Proluton Depot (Primolut Depot). Courses of treatment should be repeated frequently.

*Phase III:* Treatment should end with small doses of oestrogen and premenstrual injections of a progestogen with simultaneous recordings of basal body temperature.

Intra-uterine treatment with oestrogen.

Intra-cavitary or intra-mural oestradiol 10 to 20 mg. in crystalline suspension[25]. Treatment should be repeated after 3 to 4 weeks. Subsequently, further treatment according to Kaufmann's method.

[23] *Soskin, S., et al.:* J. Amer. Med. Ass. **114**, 2090 (1940).

[24] *Zondek, B.:* Arch. Gynäk. **161**, 284 (1936).

[25] *Husslein, H., & Gitsch, E.:* Zbl. Gynäk. **74**, 1582 (1952).

### 8. "Silent Amenorrhoea" (Cycles without menstruation)

It occasionally happens that women with secondary amenorrhoea have all the characteristics of a normal menstrual cycle (biphasic basal body temperature curve, raised pregnanediol excretion in the premenstrual phase etc.), and yet menstruation does not occur. This state of affairs is thought to be due to failure of the endometrium to react to hormonal stimuli. Diagnostic curettage can provide one with convincing evidence of proliferative endometrial activity. In cases where this is lacking or diminished, management is as with uterine hypoplasia (page 97).

### 9. Amenorrhoea with Polycystic Ovaries (Stein-Leventhal syndrome[26, 27])

The main features of this somewhat ill-defined disorder[28] are bilateral cystic enlargement of the ovaries to about 2 to 3 times their normal size, a thickened greyish-white ovarian capsule and the absence of corpora lutea. Disturbance in menstrual function (primary or secondary amenorrhoea and oligomenorrhoea) is frequently combined with hirsutism, hypoplasia of the genital tract and obesity. Urinary gonadotrophin assays have shown evidence of the fact that the anterior pituitary seems to be producing more ICSH than normal[29]. It has been possible to show that the biosynthesis of sex hormones in polycystic ovaries is abnormal, probably as a result of an endocrine disorder. The formation and excretion of testosterone and Δ-4-androstenedione is increased while that of oestrogens is reduced[30, 31]. In order to exclude adrenal causes for virilization it is suggested that the excretion of 17-ketosteroids should be determined in the following three phases[32, 33].

1. 17-ketosteroid estimation without any additional treatment.
2. 17-ketosteroid estimation with dexamethasone 5 mg. daily.
3. Measurement of urinary 17-ketosteroids with dexamethasone 5 mg. and HCG 3000 IU daily for 3 days.

During dexamethasone treatment, the only 17-ketosteroids which appear in the urine are the end result of androgen synthesis by the ovary while the corticosteroids normally present have disappeared. In cases of Stein-Leventhal syndrome, the ovarian contribution to the amount of 17-ketosteroids in urine is relatively high. During treatment with HCG it rises further. In women with normal ovarian function, hardly any 17-ketosteroids can be measured in urine during treatment with dexamethasone alone or in combination with HCG.

A further characteristic of patients with this syndrome is their sensitivity to treatment with gonadotrophins. A course of PMS and HCG can lead to ovarian haemorrhage, theca cell proliferation and ultimately fibrosis and degeneration of the ovaries.

It is not certain whether or not the characteristic ovarian pathology starts in the unborn foetus of a mother with pre-eclamptic toxaemia (and raised HCG excretion) (pages 31, 113).

Small degrees of cystic enlargement of the ovaries are not uncommon. The classical Stein-Leventhal syndrome is however only an infrequent occurrence. Many people therefore consider that these cases do not represent a uniform and single type of pathology.

#### Suggestions for Treatment

Wedge resection of the ovaries with removal of the thickened tunica albuginea and the hypertrophic ovarian stroma[34].

Some authors suggest[35] that if ovulation does not occur after operation, treatment with PMS and HCG is indicated. Anteron (Primantron) 1000 IU on alternate days x 3, followed by Primogonyl 1000 IU daily for 3 days; this treatment can be repeated on one or two occasions starting after episodes of menstrual bleeding. It should be associated with frequent bimanual pelvic examination to determine the size of the ovaries. If there is evidence of overstimulation, treatment should be discontinued.

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[26] *Stein, I. F., & Leventhal, M. L.:* Amer. J. Obstetr. Gynec. **29**, 181 (1935).
[27] *Leventhal, M. L.:* Amer. J. Obstetr. Gynec. **76**, 825 (1958).
[28] *Philipp, E., & Stange, H. H.:* Wien. klin. Wschr. **71**, 563 (1959).
[29] *Ingersoll, F. M., & McArthur, J. W.:* Amer. J. Obstetr. Gynec. **77**, 795 (1959).
[30] *Axelrod, L. R., & Goldzieher, J. W.:* J. Clin. Endocr. **22**, 431 (1962).
[31] *Kase, N., & al.:* Act. endocr. **44**, 8 (1963).
[32] *Baulieu, E. E., & al.:* J. Clin. Endocr. **23**, 374 (1963).
[33] *Jayle, M. F., & al.:* Act. endocr. **36**, 375 (1961).
[34] *Philipp, E.:* Deutsch. med. Wschr. **80**, 974 (1955).
[35] *Staemmler, H.-J.:* Arch. Gynäk. **187**, 711 (1956).

## 10. Amenorrhoea in Cases of Adreno-genital Syndrome (AGS)

Amenorrhoea may be of adrenal origin in women with marked evidence of virilization. While adrenal tumours represent acquired disease (page 133), the adreno-genital syndrome is due to a congenital disorder of the adrenals[36].

*Pathology:* The AGS is due to a disorder of the adrenal with the production of corticosteroids in insufficient amounts. This results in an increased production of ACTH by the anterior pituitary (due to a negative "feed-back" effect from peripheral hormones) and this stimulates the adrenals to produce androgens in pathological amounts (figure 48). There is an alteration in the balance between glucocorticoids and adrenal androgens with a marked increase of the latter[37]. The pathological amounts of circulating androgen, in their turn, inhibit the production of gonadotrophic hormones by the anterior pituitary. The ovaries thus lack their normal hormonal drive. It is thus obvious that amenorrhoea is only a secondary symptom. The insufficient production of glucocorticoids is due to a lack of the necessary enzyme systems. This is probably genetic in origin and constitutes the actual basis of the AGS.

*Differential Diagnosis:* Women with congenital AGS develop a male distribution of hair, generally masculine features and genital tract malformations. A uterus and ovaries are present. The chromosome constitution is female. People with AGS tend to remain small as the increased amounts of androgen lead to early epiphyseal closure.

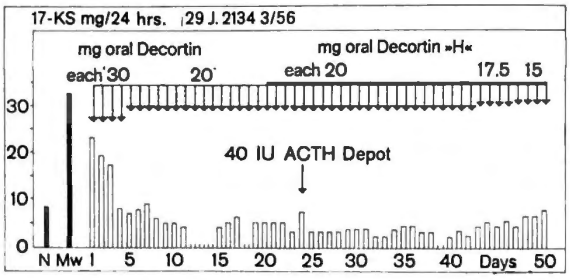



Figure 48. Adreno-genital syndrome due to adrenal hyperplasia. The 17-ketosteroid excretion falls during treatment with prednisone and prednisolone.
Normal value = N
Average value before treatment = Mw.
(*Würterle, A.:* Dtsch. Gesd.wes. 11, 1705 [1956])

[36] *Jones, H. W., & Jones, G. E. S.:* Amer. J. Obstetr. Gynec. 68, 1330 (1954).
[37] *Wilkins, L., & al.:* J. Clin. Endocr. 12, 257 (1952).

The marked increase in urinary 17-ketosteroid excretion is particularly striking. It is due to the pathological increase in androgen formation. It regresses with cortisone treatment, as this reduces the production of ACTH and hence the production of androgens by the adrenal. The urinary 17-ketosteroid excretion in patients with adrenal tumours is not affected by treatment with cortisone as the tumours are autonomous. As a result of adrenal dysfunction, patients with AGS often have increased amounts of pregnanediol and pregnanetriol in the urine[38, 39].

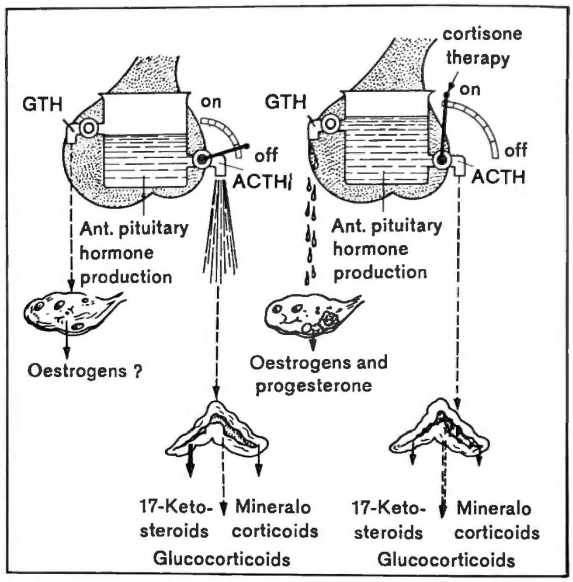



Figure 49. Schematic illustration of the adreno-genital syndrome. The abnormal adrenal is unable to secrete adequate amounts of glucocorticoids. The normal negative feed-back effect on ACTH formation by the anterior pituitary thus fails. A rise in ACTH production then leads to the increased output of androgens from the adrenals. With cortisone treatment, the amount of ACTH produced falls to normal levels while the secretion of GTH (gonadotrophic hormones) is stimulated.
(*Greenblatt, R. B.:* Fertility and steril. 8, 537 [1957])

These metabolites represent an inability of the adrenals to synthesise glucocorticoids from progesterone as in the normal course of events (page 10, tab. III).
Minor degrees of virilization combined with amenorrhoea, other menstrual disturbances or infertility may be of adrenal origin but are distinct from the marked cases of AGS which

[38] *Bongiovanni, A. M.:* Bull. Johns Hopkins Hosp. 92, 224 (1953).
[39] *Segaloff, A., & al.:* J. Laborat. Clin. Med. 45, 219 (1955).

are relatively rare[40, 41]. The former cases do not show malformations and their 17-ketosteroid excretion is not necessarily increased. Their differential diagnostic distinction from cases of ovarian virilization was discussed in a previous section (page 83). Cortisone or similar steroids may, in such cases, lead to a restoration of normal menstrual function. It may be necessary to administer them for several months before a biphasic cycle is re-established.

**Suggestions for treatment:**

1. With marked AGS:

Scherisolon (Prednisolone) tablets 10 to 20 mg. daily for prolonged periods[40, 41]. In the early days of treatment, repeated urinary 17-ketosteroid estimations are necessary in order to determine the optimum dose of prednisolone, which affects androgen metabolism and renders it normal.

2. Mild cases:

Scherisolon (Prednisolone) 5 to 10 mg. daily for several months. Menstrual bleeding tends only to occur after such an interval.

In cases where there is a history of peptic ulceration or diabetes mellitus, corticoids should only be used after advice and collaboration from a physician have been obtained (page 49).

## 11. Post-partum Amenorrhoea[42, 43]

Post-partum amenorrhoea is often very resistant to treatment and warrants special consideration. If the uterine cavity has been curetted in the puerperium, further curettage, the introduction of a sound into the uterine cavity or therapeutic trials of progesterone and later oestrogens (page 54) may be necessary in order to determine whether any potentially functional endometrium is present. After uterine amenorrhoea has been excluded by these measures, it can be assumed that lack of menstruation is due to endocrine disorder resulting from a disturbance in the hypothalamic-anterior pituitary axis[42, 43].

Different types of post-partum amenorrhoea have been described:

*Sheehan's Syndrome*[44]

This unusual occurrence is seen after difficult deliveries in which excessive blood loss has occurred. This is followed by necrosis of a large portion of the anterior pituitary (60 to 90 per cent) and the gland is ultimately replaced by connective tissue. The symptom complex which may be very variable depends on the amount of endocrine tissue which necroses. Myxoedema, hypo-adrenalism, loss of pubic and axillary hair, diabetes insipidus, anorexia nervosa and obesity have all been observed.

Examination of the endometrium, radio-iodine uptake studies, measurement of the urinary 17-ketosteroids and ketogenic steroids, and the Thorn test etc. provide information with which to assess the degree of pituitary insufficiency[45]. This must be known before suitable substitution therapy can be prescribed. Post-mortem studies have shown that it is incorrect to consider all cases of post-partum amenorrhoea demonstrating metabolic disturbances as cases of *Sheehan's* syndrome. This diagnosis should be reserved for circumstances in which there is post-partum necrosis of the anterior pituitary with its corresponding symptoms.

*Hypothalamic post-partum amenorrhoea*[42]

With the exception of the rather rare cases already described, women with post-partum amenorrhoea do not show organic changes in the ovary or the pituitary. Not infrequently, metabolic disturbances resulting in anorexia nervosa or obesity may be seen. The gonadotrophin excretion tends to be diminished. These findings suggest that in most cases, post-partum amenorrhoea is caused by dysfunction of the anterior pituitary resulting from a disturbance in hypothalamic stimuli. Details about this mechanism are not yet known. It is possible that its cause is a failure of the hypothalamus to switch over to normal function after the end of pregnancy.

The prognosis of post-partum amenorrhoea is uncertain although it is nearly always due to a functional type of disturbance. Before treatment, a progesterone test in which 2 doses of progesterone 20 mg. are given

[40] *Kupperman, H. S., & al.:* The Endocrine Society, 47. Tagung (1955).

[41] *Weißbecker, L.:* M.kurse ärztl. Fortbild. 6, 369 (1956).

[42] *Staemmler, H.-J.:* Gestörte Regelung der Ovarialfunktion, Springer-Verlag 1964.

[43] *Weiser, P., & Kümmel, J.:* Med. Klin. 57, 1893 (1962).

[44] *Sheehan, H., & Summers, V.:* Quart. J. Med. 18, 319 (1949).

[45] *Schwarz, K.:* Münch. med. Wschr. 104, 777 (1962).

should be made in order to determine whether or not there is total failure of sex hormone production.

**Suggestions for Treatment:**

1. Anteron (Primantron) 1000 IU i.m. x 3 on alternate days. Primogonyl 5000 IU on alternate days x 3 commencing on the same day as the last Anteron injection (figure 45, page 81). Possibly thyroxine, ACTH or prednisone in combination with desoxycorticosterone acetate, depending on the type of replacement therapy made necessary by peripheral endocrine gland failure.

2. If gonadotrophin treatment has no results or only meets with transient success, replacement therapy with sex hormones should be given to younger women in order to prevent the occurrence of genital or extra-genital atrophy as well as "vegetative" disturbances. Progynon Depot (Primogyn Depot) 10 mg. and, after 2 weeks, Progynon Depot (Primogyn Depot) 10 mg. with Proluton Depot (Primolut Depot) 250 mg. should be given in order to produce the hormone pattern of a menstrual cycle.

3. In older women, 1 ampoule of Primodian Depot every 3 to 4 weeks.

Table 18. *Summary of Findings with Gonadal Dysgenesis*

(*Prader, A., & Töndury, G.:* Klinik der inneren Sekretion 673 [1957])

Hypogonadism is the only consistent finding; all other signs are present in variable degrees.

| Neonatal period | Infancy and Childhood | Adolescence | Maturity |
|---|---|---|---|
| Lymphatic oedema of hands and feet | | | |
| Signs of degeneration or malformation → | | | |
| | Dwarfism → | | |
| Pterygium colli<br>Cutis laxa | Normal or slightly retarded bone development | | Late epiphyseal closure.<br>Span greater than height |
| Malformations of eyes and ears | Tetrahedron chest → | | |
| Micrognathia | Wide separation of nipples | | |
| Sphynx-like or wrinkled facies | hypergonadotrophic Hypogonadism → | | |
| Hypoplastic nipples<br>Cubitus valgus | Primary Amenorrhoea | | Osteoporosis |
| Skeletal and spinal malformations | No breast development | | |
| Isthmusstenosis | Hypoplastic labia minora | | |
| Renal malformations | Pubic hair sparse and delayed in appearance | | |
| Hypertension of uncertain origin and other abnormalities | Urine:<br>Gonadotrophins ↑↑<br>17-Ketosteroids ↓<br>Oestrogens ↓↓ | | |

## 12. Amenorrhoea and Galactorrhoea[46–48]

Amenorrhoea, associated with galactorrhoea, may occur following delivery. Frequently it may be associated with obesity and atrophy of the uterus and vagina (*Chiari-Frommel* syndrome). The urinary gonadotrophin excretion is not increased. The excretion of oestrogens is very low. It must be assumed that the disorder is due to some hypothalamic or anterior pituitary factor.

Rarely this condition may occur in circumstances which are not related to a previous delivery. In the absence of preceding pregnancy, it is assumed that galactorrhoea is due to an abnormally high production of prolactin. Detailed examination often reveals a tumour of the anterior pituitary (chromophobe adenoma). Thus each such case should be investigated carefully. In suitable cases, surgical removal of the anterior pituitary tumour should be undertaken and followed by treatment with steroid hormones according to the recommendations of *Kaufmann*. This may diminish the excessive flow of milk and prevent genital tract atrophy.

## 13. Amenorrhoea with Dwarfism and Ovarian Failure

Ovarian agenesis = *Turner's* syndrome[49–51], Ovarian dysgenesis (page 79).

With dwarfism, generally retarded development, absent secondary sex characteristics and amenorrhoea, complete ovarian failure (ovarian agenesis, *Turner's* syndrome) must be considered with the presence of rudimentary ovaries (ovarian dysgenesis) as a further possibility (table 18).

Webbing of the neck, cubitus valgus, cutaneous naevi and skeletal dysplasias are sometimes seen[52].

It has been shown that the failure of ovarian development is due to absence of an X sex chromosome. An XY sex chromosome constitution is also sometimes seen but is rare[53, 54].

The following special investigations are necessary:

Cytological examination of the vaginal epithelium. With ovarian dysgenesis, even large doses of gonadotrophin do not evoke an oestrogen response.

Measurement of urinary gonadotrophin (the values are usually raised). Tumours of the hypothalamic and anterior pituitary areas should be excluded by X-ray studies of the sella turcica and other appropriate diagnostic tests.

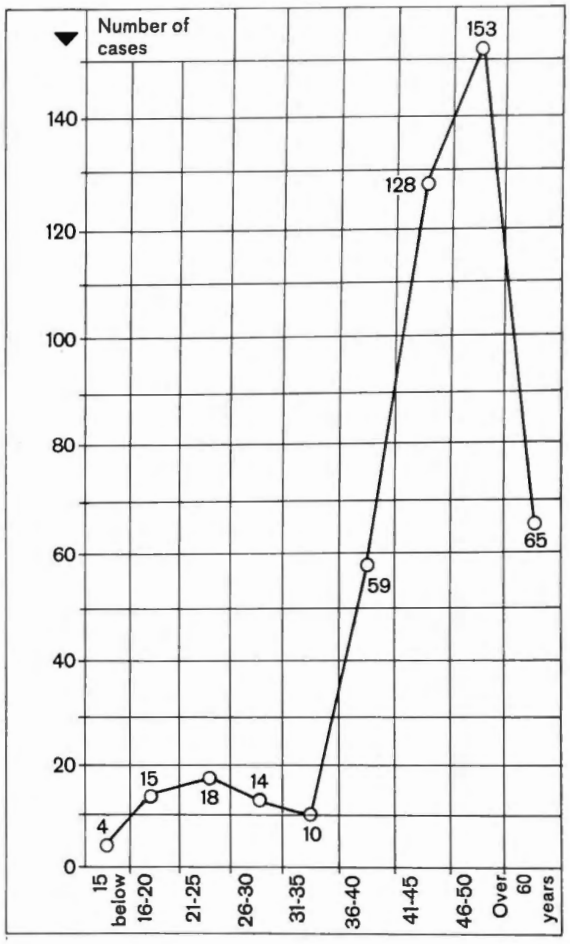



Figure 50. Age distribution of cases of cystic glandular hyperplasia with proven cystic follicles.
(*Tietze, K.* in Seitz-Amreich: Biologie und Pathologie des Weibes, Berlin-Wien II, 2, 614 [1952])

Exploratory laparotomy may also be necessary. Radiological study of the epiphyseal centres which persist for an abnormally long time. Chromosomal sex determination: it may not be possible to demonstrate a sex chromatin body (page 60)[55], or a patient's karyotype may reveal an XO or an XY sex chromosome constitution. Treatment should depend on

[46] *Argonz, J., & del Castillo, E. B.:* J. Clin. Endocr. 13, 79 (1953).
[47] *Zondek, H.:* Die Krankheiten der endokrinen Drüsen, Basel 1953.
[48] *Forbes, A. P., & al.:* J. Clin. Endocr. 14, 250 (1954).
[49] *Ehrengut, W.:* Zschr. Kinderhk. 75, 224 (1954).
[50] *Philipp, E.:* Dtsch. med. Wschr. 77, 1209 (1952).
[51] *Overzier, C., & Linden, H.:* Gynaecologia 142, 215 (1956).
[52] *Schönenberg, H., & al.:* Zschr. Kinderhk. 79, 383 (1957).
[53] *Zander, J.:* Mkurse ärztl. Fortb. 12, 432 (1962).
[54] *Hauser, G. A.:* Internist 4, 6 (1963).
[55] *Schönenberg, H., & al.:* Ärztl. Wschr. 12, 697 (1957).

the patient's somatic development rather than on the cytogenetic determination of sex, the results of which should not be revealed to the family members in cases where it turns out to be male. Skeletal growth can be enhanced by oestrogens as can the growth of the genital tract in limited measure.

**Suggestions for Treatment:**

Substitution therapy with oestrogens and progestogens. Injections of Progynon Depot (Primogyn Depot) and also Proluton Depot (Primolut Depot) on alternate weeks with the aim of achieving menstrual bleeding in cases of secondary amenorrhoea (page 78).

### d) Dysfunctional Bleeding with Persistent Cystic Follicles

(Metropathia haemorrhagica)

*Definition.* Irregular, prolonged bleeding with very variable intervals of freedom between them are the hallmark of dysfunctional bleeding. These cases are known as pubertal menorrhagia (page 71) and climacteric bleeding (figure 50) in the early and late years of sexual maturity, respectively. In the normal, sexually mature woman a follicle begins to develop at the end of a menstrual period. This ruptures on the 12th to 14th day of a menstrual cycle and is then transformed into a corpus luteum (page 32). At the end of the life of the corpus luteum, menstrual degeneration of the endometrium occurs. This sequence depends on a drive from the anterior pituitary.

In women with dysfunctional bleeding due to an as yet ill-understood disturbance of the hypothalamic pituitary-ovarian axis, follicles ripen and produce increasing amounts of oestrogen. These follicles do not, however, rupture but persist. During the persistent follicle's life-span, oestrogens are continuously being produced (figure 51). They cause pathological endometrial proliferative activity characterised by an increase in its thickness and by dilatation of its glands (cystic glandular hyperplasia)[56, 57]. After a time, the formation of oestrogens is insufficient to maintain the pathological endometrial proliferation. The result is endometrial bleeding which is usually of slow onset and stems from capillaries which are very sensitive to falls in oestrogen levels[58].

There are also variations of the classical picture of dysfunctional bleeding just presented, in which the endometrium shows normal proliferative activity or even early secretory changes. In these cases, the mechanism by which abnormal bleeding occurs is uncertain.

The bleeding which occurs cannot be regarded as normal menstruation for the following reasons:

At the onset of bleeding the endometrium shows cystic glandular hyperplasia instead of secretory changes.

The endometrium is not shed down to the basal layer, bleeding only occurs from its surface without significant reduction in its thickness.

Physiological regeneration and proliferation of the endometrium do not occur. Bleeding lasts much longer than normal. It ultimately leads to necrosis and complete shedding of the endometrium.

*Clinical picture and diagnosis of dysfunctional bleeding.* The diagnosis can be made with considerable accuracy from the history, general and pelvic examination and some special investigations:

*History.* The disorder is relatively common in women who are at the beginning (16 to 20 years of age) or at the end (over 40 years of age) of the reproductive era. A short spell of amenorrhoea often precedes an episode of abnormal bleeding[59]. The episode of bleeding is often prolonged and heavy, sometimes it may be relatively slight. Because there is no corpus luteum, the basal body temperature curve which precedes an episode of bleeding is often monophasic.

*Gynaecological examination.* There are no abnormal pelvic physical signs as a rule. Sometimes, moderate cystic enlargement of the ovaries may be palpable. Differential diagnoses of importance are threatened abortion, ectopic pregnancy, uterine polyps, small fibroids or an endocervical carcinoma[60].

[56] *Schröder, R.* in *Veit-Stoeckel:* Handbuch der Gynäkologie, Berlin I, 2 (1928).

[57] *Meyer, R.* in *Henke-Lubarsch:* Handbuch der speziellen pathologischen Anatomie u. Histologie, Berlin VII,1 (1930).

[58] *Allen, W. M.:* South Med. J. 44, 817 (1951).

[59] *Kaufmann, C., & Giesen, W.:* Arch. Gynäk. 170, 457 (1940).

[60] *Jakobs, W. M., et al.:* Amer. J. Obstetr. Gynec. 71, 1322 (1956).

*Histological examination of the endometrium*[61]. The endometrium seldom shows secretory changes and even in the first days of bleeding presents a picture of cystic glandular hyperplasia, i.e. cystic dilatation of the gland ducts, and epithelial changes which are characterised by enlargement and crowding of the nuclei[64]. After bleeding of several weeks' duration it is often not possible to obtain endometrium. It has been "bled away"[62].

The urinary oestrogen excretion is relatively high. According to *Brown*[63] the 24-hour urine contains an average of 30 to 40 γ. The pregnanediol content of 24-hour urines is insignificant.

Treatment with oestrogen-progestogen combinations serves also to confirm the diagnosis. If bleeding stops within 48 hours of commencing treatment[65, 66] a diagnosis of dysfunctional bleeding is highly likely. If it does not, it is probable that there is an organic cause which must be looked for by further diagnostic measures.

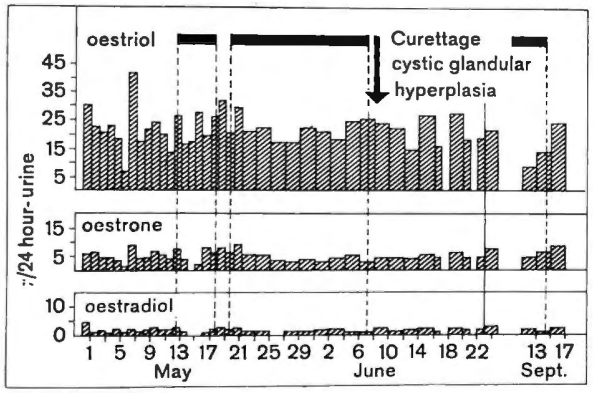



Figure 51. Variable and sometimes raised excretion of oestrogens in a 27-year-old patient found to have cystic glandular hyperplasia of the endometrium at curettage on 8 th June

(*Brown, J. B., et al.:* J. Obstetr. Gynaec. 66, 177 [1959])

*Hormone treatment versus curettage*

The age of the patient, the history and the findings determine therapy. In young girls, hormone therapy constitutes the treatment of choice (page 71) and curettage should, wherever possible, be avoided.

In the more mature patient or in women approaching the menopause there are two main methods of management: curettage and hormone therapy. If an organic lesion, particularly an endocervical carcinoma cannot be excluded by history, general and pelvic examination, curettage must always be the first measure. It not only may arrest bleeding but also provides information about the contents of the uterine cavity.

In many cases, however, one can make do with hormone treatment alone. Its differential diagnostic and therapeutic values have been demonstrated[67]. In cases with recurrent bleeding and where the endometrial histology has already been studied, hormone therapy is always indicated provided operation or radiotherapeutic measures are not preferable.

*Hormone therapy—method of action*

Progestogens alone or in combination with oestrogens exert a haemostatic effect on the endometrium within about 24 hours. At this time, no secretory changes in the endometrium can be detected. It is therefore a change in the capillaries which occurs with such predictable certainty. After 10 days of treatment, the endometrium begins to show secretory changes which may be rather patchy.

When hormone therapy is discontinued, menstrual shedding of the endometrium occurs. This process has also been called "medical curettage"[68]. With this, the duration of bleeding is usually 4 to 8 days. It is sometimes heavier than a normal menstrual period, particularly in women with arteriosclerosis and hypertension. In young patients a coagulation defect is sometimes present (thrombopenia). "Secale" preparations as well as oestrogens and testosterone in high doses (testosterone proprionate 50 mg. on 2 consecutive days) may be used to reduce the blood loss which follows withdrawal of hormones.

**Suggestions for treatment:**
(standard therapy)[69]

3 tablets of Primolut N daily for 10 days. The injection of a "depot-mixture" (Primosiston in oily suspension) is not advisable as the subsequent hormone withdrawal bleeding tends to be severe (page 45).

[61] *Ober, K. G.*, from Labhart, A.: Klinik der Inneren Sekretion, Berlin 1957, 533.
[62] *Will, J.:* Med. Klin. 52, 137 (1957).
[63] *Brown, J. B., & al.:* J. Obstetr. Gynaec. 66, 177 (1959).
[64] *Buschbeck, H.:* Dtsch. med. J. 14, 275 (1963).
[65] *Rauscher, H., & Romberg, G.:* Zbl. Gynäk. 78, 2002 (1956).
[66] *Boschann, H.-W.:* Geburtsh. u. Frauenhk. 15, 1070 (1955).
[67] *Ober, K.-G.:* Dtsch. med. Wschr. 80, 552 (1955).
[68] *Albright, F.:* J. Maine Med. Ass. 29, 235 (1938).
[69] *Will, J.:* Med. Klin. 52, 137 (1957).

*Special recommendations*

❶ Because of its method of action, hormone treatment must be applied over a period of 10 days. A poorly informed patient might interrupt therapy just because the bleeding has stopped. This leads to recurrence of abnormal bleeding rather than to normal menstrual endometrial shedding.

❷ If the bleeding has not diminished within 48 hours of starting tablets, it is probable that it is of organic origin (a polyp, fibroid, abortion, ectopic pregnancy or endocervical carcinoma). Further diagnostic measures are then advisable. In addition to a careful repeat examination, a diagnostic curettage should be made.

❸ Bleeding after abortion and delivery is usually due to endometritis. The response to combined oestrogen-progestogen therapy is usually incomplete and therefore high doses of oestrogen should be used in treating these cases (page 117).

❹ Repeat Primolut N therapy "just because treatment has not helped" is contra-indicated. With very long-term bleeding, it is probable that insufficient endometrium is left to respond to progestogens. It has been shown that in such circumstances the following treatment is of value:

**Treatment** for bleeding of long duration (over 3 weeks[68, 69, 70]). Oestradiol benzoate 10 mg. by intramuscular injection. Progynon Depot (Primogyn Depot) 10 mg. 2 days later. After 7 days: Progynon Depot (Primogyn Depot) 10 mg. and Proluton Depot (Primolut Depot) 250 mg. both by intramuscular injection.
After a further 7 days: Proluton Depot (Primolut Depot) 250 mg. by intramuscular injection.
Menstrual bleeding usually occurs 8 days after the last injection (figure 52).

*Prevention of recurrence*

As long as the menstrual cycle remains monophasic there is danger of recurrent abnormal bleeding[71]. A period of amenorrhoea may indicate recurrent cystic glandular changes in the endometrium and may give warning that dysfunctional bleeding is going to reappear.

[70] *Froewis, J., & Ulm, R.:* Med. Klin. **53**, 1652 (1958).
[71] *Jann, R.:* Schweiz. med. Wschr. **86**, 1221 (1956).

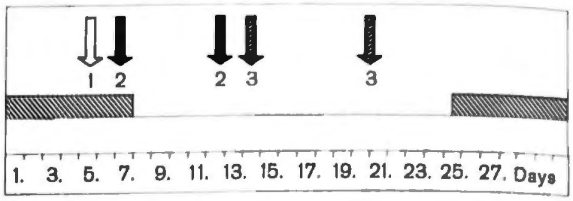



Figure 52. Prolonged bleeding arrested by hormone therapy. Oestradiol benzoate 10 mg. (1) followed 2 days later by 10 mg. oestradiol valerate (2). A second injection of oestradiol valerate (2) was injected on day 12. Secretory changes are produced by two separate injections of 125 mg. progestogen depot (3) each, (Proluton Depot, Primolut Depot).

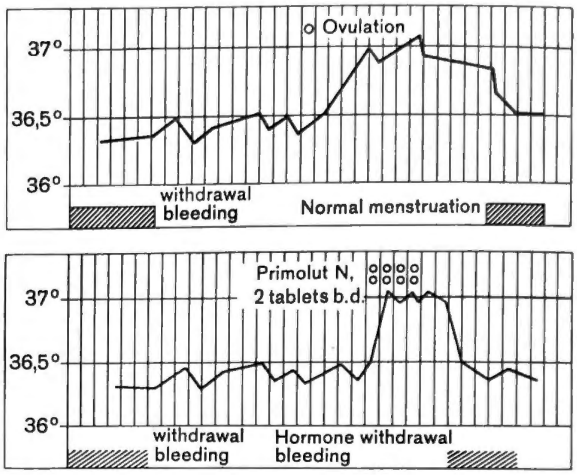



Figure 53. Prevention of recurrent functional bleeding by giving 2 tablets of Primolut N daily on 4 consecutive days during a cycle with a monophasic temperature curve.

In order to prevent recurrent dysfunctional bleeding it is advisable to keep an eye on the early morning temperature. If the cycle remains monophasic, it is advisable to aim at producing withdrawal bleeding by giving progesterone 20 to 40 mg. or 2 tablets of ethinyl-nortestosterone (Primolut N) for 4 days (figure 53). Such bleeding does not last so long nor is it as heavy as recurrent dysfunctional bleeding. If patients with monophasic cycles tend to start bleeding much before 28 days are up, treatment with Anovlar 21 (1 tablet daily from the 5th to the 25th days of the menstrual cycle) may prevent more serious trouble[72].
The prognosis with dysfunctional bleeding depends on age. It is good in the very young (page 71) and in those who are more mature. In the years before the menopause, cystic glandular hyperplasia due to persistent cystic follicles is to be interpreted as a failure of the ovary's reproductive function. The danger

[72] *Peeters, F., & al.:* Scalpell **114**, 1111 (1961).

of recurrent dysfunctional bleeding is only transient as anovulatory cycles are often followed by endocrine failure of the ovaries and, of course, the menopause.

### e) The Anovulatory Cycle

In spite of failure of ovulation, a patient's cycle may *appear* to be more or less regular. An absolutely normal cycle shows a biphasic temperature curve and is thus not anovulatory. As with dysfunctional bleeding, the developing follicles persist. While these may ripen at regular intervals, their rupture does not take place. The life-span of the cystic follicle is relatively brief so that the full-blown picture of cystic glandular hyperplasia, described previously, does not have time to develop.

Bleeding, which is strictly speaking not menstrual, occurs about once a month in response to a fall-off in oestrogen excretion. There are no secretory changes in the endometrium and the bleeding is from proliferative epithelium, being of the oestrogen withdrawal type. The anovulatory cycle is mainly seen at the beginning and end of the reproductive era. In many women, occasional anovulatory cycles also occur in the second and third decades. A disturbance can only be considered serious if observation over a long period (at least six months) shows persistent absence of ovulation.

A diagnosis is most easily established by measurements of basal body temperature. Anovulatory cycles should be suspected in all women with infertility and irregular bleeding. Premenstrual urinary pregnanediol estimations (if they are under 1 mg. per 24 hours) and premenstrual endometrial biopsy (if it shows proliferative changes only) are important bits of evidence which favour the diagnosis.

Treatment need only be considered if infertility is a problem or if bleeding continues for too long a time.

**Suggestions for Treatment:**

1. With infertility (page 101):

Anteron (Primantron) 1000 IU on the 5th, 7th and 9th days of the cycle, and Primogonyl 1000 to 5000 IU on the 9th, 11th and 13th days of the cycle.

2. Bleeding of long duration:

1 tablet of Primolut N daily from the 18th to 26th days of the cycle x 2.

### f) Disturbances of Rhythm in the Presence of Ovulation

Menstrual abnormalities may only be considered as disturbances of rhythm if ovulation and the luteal phase of the cycle are not lost. In the presence of biphasic cycles, periods at too frequent or too infrequent intervals can be regarded as variations of normal function. If infertility is present, a disturbance of rhythm should be carefully investigated with evidence from basal body temperature records, examinations of cervical mucus and vaginal cytology.

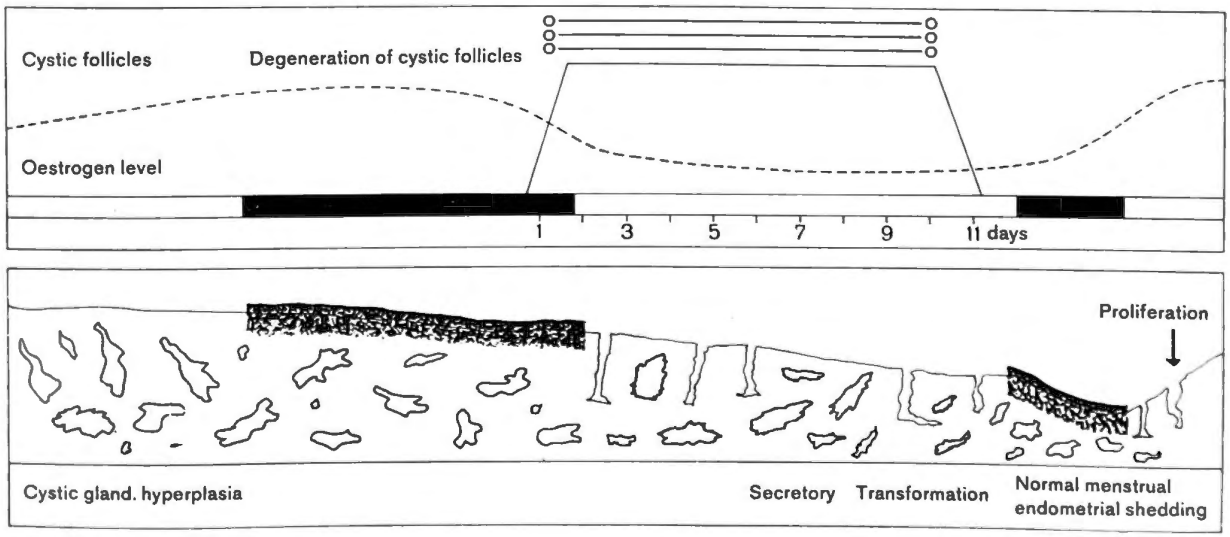



Figure 54. The mechanism of bleeding with cystic glandular hyperplasia. Effect of treatment with 3 tablets of Primolut N daily for 10 days.

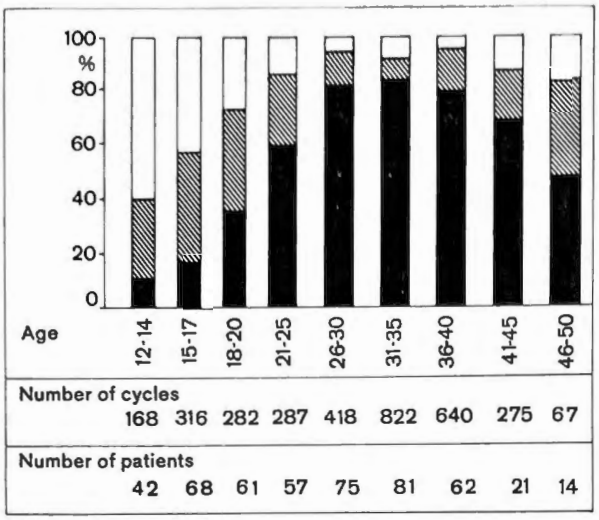



Figure 55. The incidence of anovulatory cycles at different ages.

unshaded → anovulatory cycle
cross-hatching → abbreviated luteal phase
black shading → normal cycle.

(*Döring, G. K.*, Arch. Gynäk. 199, 2:115 [1963])

## 1. Oligomenorrhoea

If menstrual bleeding occurs at infrequent intervals, it is the follicular phase which is usually prolonged while the luteal phase of the cycle is of normal duration[73].

In making a differential diagnosis, it is important to discover whether or not ovulation is occurring (see Infertility, page 101). The measurement of waking temperatures is of utmost importance in this respect.

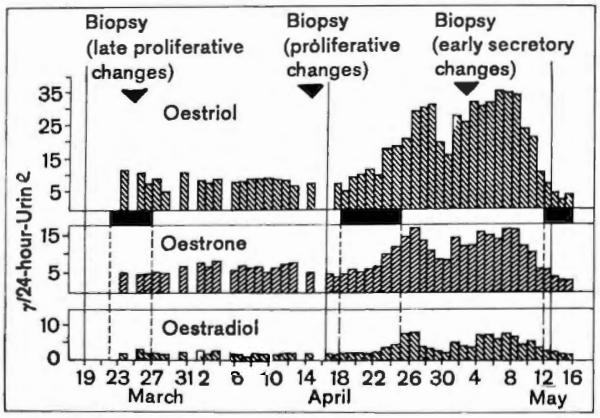



Figure 56. Oestrogen excretion pattern in a 26-year-old woman. The first cycle is anovulatory. Oestrogen excretion is persistently low. The second cycle shows a biphasic pattern. Oestrogen excretion shows two peaks. The bleeding on 12 th May represents normal menstruation.

(*Brown, J. B., & al.*: J. Obstetr. Gynaec. 66, 177 [1959])

[73] *Knaus, H.*: Zbl. Gynäk. 66, 737 (1942).

In most cases, there is no indication for therapy. It would be logical to bring about the rupture of the follicle by treatment with gonadotrophic hormones. As experience with this form of treatment is still very limited it is not discussed in detail (see treatment with gonadotrophins, page 91).

Sex hormones can be used in cyclical fashion, as with amenorrhoea, in the hope that they will bring about some alteration in the hypothalamic-anterior pituitary system resulting in normal ovarian drive with normal menstrual function.

### Suggestions for Treatment:

Progynon Depot (Primogyn Depot) 10 mg. on the 6th and 18th days of the cycle and Proluton Depot (Primolut Depot) 250 mg. on the 18th day of the cycle.

Several repeat courses of treatment.

An episode of bleeding can be brought forward in the following way[74]: 1 tablet of Primolut N daily from the 5th to the 14th days of the cycle x 3. Bleeding begins between the 15th and 17th day and the next menstrual period occurs 4 weeks later.

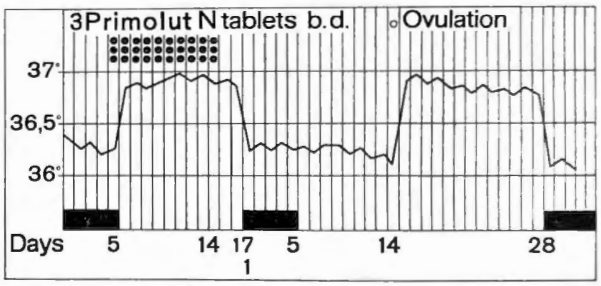



Figure 57. Scheme to show how the onset of menstruation can be accelerated. Note temperature curve.

Prolonged intervals between periods, with heavy bleeding when they occur, probably indicate persistent follicles rather than oligomenorrhoea (page 88). The basal body temperature curve is of differential diagnostic importance. Treatment is the same as that used for prophylaxis in cases of dysfunctional bleeding with cystic glandular hyperplasia (page 88).

If the occasional menstrual period is delayed in an otherwise normal cycle, it is possible that an early abortion has occurred.

There is no agreement about the theory that menstruation may be delayed by spontaneous prolongation of the life of the corpus luteum. Halban was the first to suggest this possibility,

[74] *Kaiser, R.*: Geburtsh. u. Frauenhk. 22, 122 (1962).

calling it the state of "persistent corpus luteum function". This form of oligomenorrhoea must be very rare. It certainly requires no treatment.

**2. Polymenorrhoea (periods occurring too frequently)**

(Pubertal polymenorrhoea: page 71)

Two types of polymenorrhoea can be recognized and they are most easily distinguished by basal body temperature curves.

*a) Polymenorrhoea due to a short follicular phase*

Although the proliferative phase of the cycle is less than 14 days, the luteal phase is of normal duration. Provided that menstrual bleeding is not too heavy and is not complicated by anaemia, this type of disturbance does not necessarily require treatment. Infertility is not present.

**Suggestions for Treatment:**

Ovulation may be delayed for several days by administering oestradiol benzoate 10 mg. by intramuscular injection on the 4th to 6th days of the cycle (figures 58, 59).

*b) Polymenorrhoea due to an abbreviated luteal phase*

This type of polymenorrhoea is of practical importance as it is almost always associated with infertility (page 101). The inadequate life of the corpus luteum, caused by some imbalance between the anterior pituitary and the ovaries, is easily recognized by a study of the basal body temperature record (figure 60).

The reduced and too brief secretion of progesterone leads to incomplete premenstrual transformation of the endometrium which makes a poor environment for nidation of the fertilized ovum. The pregnanediol excretion is correspondingly reduced.

A simple and effective method of treating this disorder is the use of progestogens and oestrogens starting shortly before the expected onset of a menstrual cycle.

**Suggestions for Treatment:**

1. With a luteal phase which is reduced to 10 days, the injection of a mixture of 17α-hydroxy-progesterone caproate 250 mg. and oestradiol benzoate 10 mg. (i.e. one ampoule of Primosiston) should be administered on the 5th or 6th day after the first rise in basal body temperature. Bleeding then occurs on the 14th day after a thermal shift which indicates that the secretory phase of the cycle has lasted 14 days (figure 61).

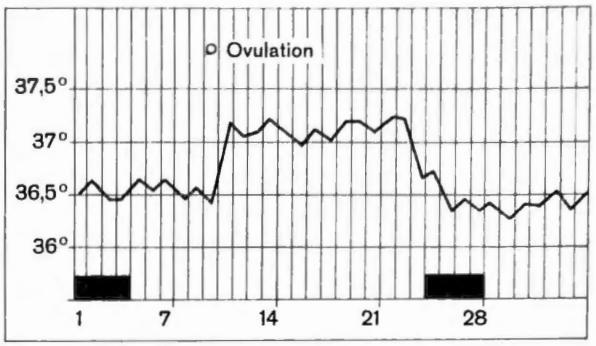



Figure 58. Shortened proliferative phase.

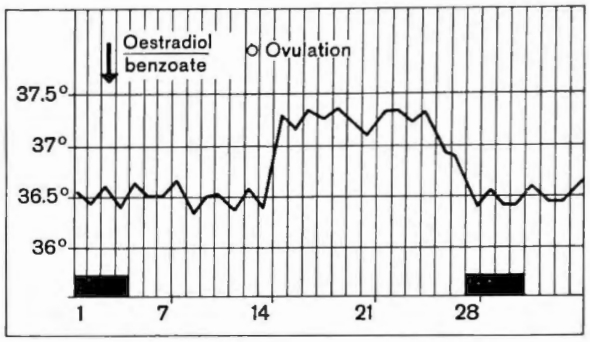



Figure 59. Delaying ovulation with oestradiol benzoate.

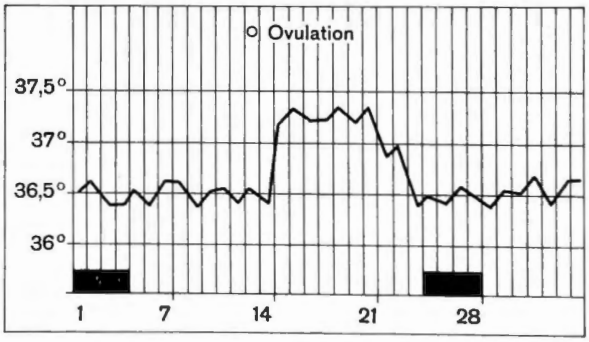



Figure 60. Shortened secretory phase.

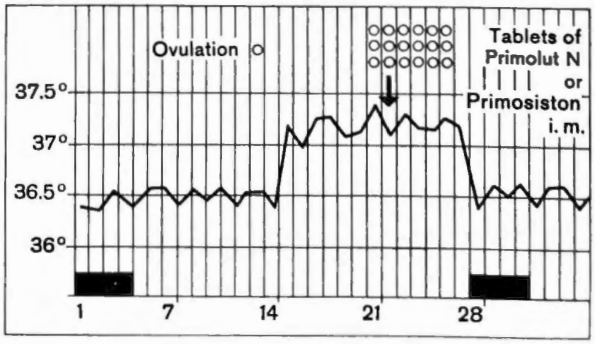



Figure 61. Suggested method of prolonging the secretory phase by using Primosiston or Primolut N.

2. Three tablets of Primolut N daily from the 21st to 26th days of the cycle (figure 61)[75]. The use of chorionic gonadotrophin (stimulation therapy) in order to prolong the life of the corpus luteum can also be considered.

3. HCG (Primogonyl) 5000 IU × 3 between the 20th and 24th days of the cycle[76, 77].

*Delaying menstruation*[78, 79]

For reasons of convenience (e.g. a sporting event or a journey) it may be possible to delay menstruation in patients who usually have a normal cycle by employing the treatment described in paragraph 2 above. For certain success, it is necessary to start treatment 3 to 4 days before the expected onset of menstruation.

**Example:** A woman with a 28-day cycle wishes her period to be delayed for 8 days. Primolut N, one tablet 3 times daily from the 25th to 34th days of the cycle should be given. Ovulation and menstruation occur in the normal way in the subsequent cycle.

### g) Abnormal Bleeding at Regular Intervals

#### 1. Ovulatory Bleeding

Although persistent intermenstrual bleeding usually has an organic cause (a polyp or carcinoma), a slight loss at the time of ovulation usually has endocrine causes. It is often associated with the so-called 'Mittelschmerz'. It probably represents a form of oestrogen withdrawal bleeding due to a transient reduction in the secretion of oestrogens. Traces of blood are frequently seen in the cervical mucus about the time of ovulation and should not be considered pathological[80].

**Treatment:**

One injection of oestradiol benzoate 5 mg. shortly before the expected occurrence of intermenstrual bleeding (perhaps on the 12th day of the cycle) should be sufficient to counter the temporary deficit of oestrogens and to prevent intermenstrual loss (figure 62).

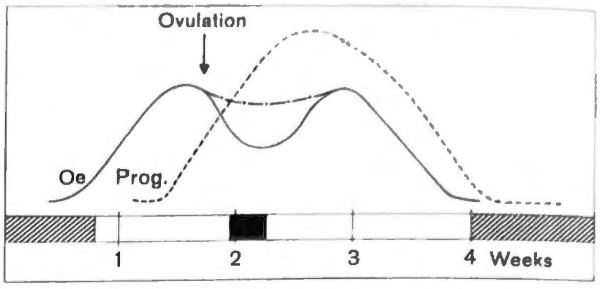



Figure 62. Pattern of oestrogen and progesterone production in a patient with ovulatory bleeding. The dip in oestrogen production at the time of ovulation can be countered by giving one injection of oestradiol benzoate 5 mg. ↓ on about the twelfth day of the cycle.

#### 2. Premenstrual Bleeding

Slight bleeding up to 10 days before the start of a menstrual period is again usually due to endocrine causes. It should not be confused with the different types of polymenorrhoea. It is due to an unusually early reduction of oestrogen secretion by a corpus luteum which is otherwise functioning normally and still producing progesterone[80a]. The temperature curve is biphasic.

**Treatment:**

Ethinyl oestradiol can be used to restore the temporarily disturbed balance between progesterone and oestrogens and thus to prevent premenstrual bleeding.

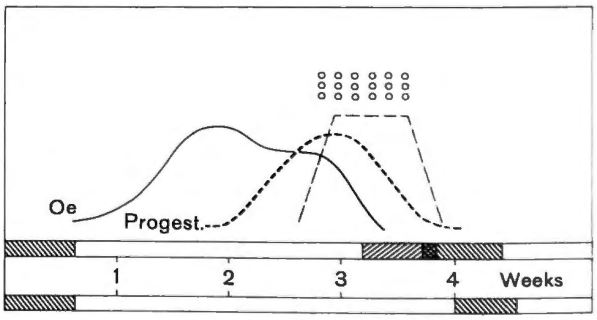



Figure 63. Pattern of oestrogen and progesterone formation with premenstrual bleeding. One tablet of Progynon C (Primogyn C) (O) three times daily until the 26th day of the cycle prevents the premature fall in the level of oestrogenic hormone. Premenstrual bleeding therefore does not occur.

Treatment starts shortly before bleeding is expected to commence with one tablet of ethinyl oestradiol 0.02 mg. three times daily until about the 26th day of the cycle (figure 63). In cases where the secretion of progester-

[75] *Husslein, H., & Hofbansl, W.:* Wien. klin. Wschr. **71**, 821 (1959).
[76] *Palmer, M. R.:* Bull. Ass. gynec. obstetr. **2**, 21 (1950).
[77] *Lambert, G.:* Gynéc. et obstétr. **48**, 3 (1949).
[78] *Hofbansl, W., & Baumgarten, K.:* Wien. klin. Wschr. **73**, 557 (1961).
[79] *Döring, G. K.:* Dtsch. med. Wschr. **88**, 1721 (1963).
[80] *Bromberg, Y. M., & Bercoroci, B.:* Fertility and steril. **7**, 71 (1956).
[80a] *Weber, M.:* Geburtsh. u. Frauenhk. **14**, 710 (1954).

one, as judged from a study of the basal body temperature curve, is deficient 2 tablets of Primolut N may be added to the daily dose of hormones.

### 3. Postmenstrual Bleeding

Not infrequently, slight bleeding or smears of blood may be observed just after a menstrual period or after a lapse of one or two days. This may mean deficient endometrial regeneration[81]. The response of the endometrium to hormonal stimuli may be diminished in women who have had repeated curettage, many deliveries or an active endometritis[82].

**Treatment:**

One tablet of Progynon C (Primogyn C) daily for 8 days starting on the 2nd day of the cycle.

### 4. Hypermenorrhoea (page 71)

Increased bleeding with regular, biphasic cyles is often due to fibroids, polyps, pelvic congestion with a retroverted uterus or atherosclerosis. An abnormality of the haemopoietic system (thrombopenia) or hypertension can also cause hypermenorrhoea. It must further be noted that inadequate contractility of uterine muscle can be the reason for heavy bleeding during menstrual periods in the absence of any other organic disorder. It is particularly the small, hypoplastic uterus which shows this tendency. In cases of hypermenorrhoea in which organic disease has been excluded by curettage, the use of Secale preparations may be considered:

**Hormone Treatment:**

1. One ampoule of Testoluton forte (Primofemin forte) x 3 during heavy blood loss.

2. Three tablets of Primolut N daily from the 20th to 26th days of the cycle.

3. Treatment of uterine hypoplasia with oestrogens and progestogens (page 97).

Menorrhagia, or an increase in the duration of a period is unusual in circumstances where the cycle is still regular. This is treated as in No. 2 above.
Poly-hypermenorrhoea (bleeding which is excessive and too frequent) has been considered on page 71.

[81] *v. Mattenbach, W.:* Dtsch. med. Wschr. **81**, 2035 (1956).
[82] *Tietze, K.:* Dtsch. med. Wschr. **58**, 1876 (1932).

### 5. Hypomenorrhoea

In women with a regular cycle and abnormally scanty periods it is seldom possible to find evidence of ovarian disturbance[83]. The basal body temperature curve is biphasic. In spite of this, it cannot be denied that many of these cases may have an endocrine cause particularly as obesity and premenstrual symptoms may often be present. The possible role of uterine factors must also be considered. Endometrial tuberculosis, partial destruction of the endometrium by "Atmokausis" or too thorough curettage may have occurred. In such cases, thin endometrium with scanty glands may be obtained at premenstrual curettage.

**Treatment:**

Hypomenorrhoea is usually resistant to treatment. Obese patients should reduce weight by diet. If curettage shows poorly developed endometrium, cyclical therapy which is the same as that used in uterine hypoplasia (page 97) is indicated.

### h) Dysmenorrhoea

Dysmenorrhoea is a symptom with many possible causes[84]. It often bears a close relationship to psychological factors and to function of the autonomic nervous system. A distinction can be made between organic dysmenorrhoea (fibroids, endometriosis, cervical stenosis), functional dysmenorrhoea (in cases of uterine hypoplasia with parametropathia spastica and with general dystonia of the autonomic nervous system) and dysmenorrhoea without demonstrable cause or findings (essential dysmenorrhoea).
It is useful to distinguish between cases of primary and secondary (acquired) dysmenorrhoea[85]. There is often an organic cause for secondary dysmenorrhoea. The non-organic, functional types of dysmenorrhoea are only seen in patients with a biphasic basal body temperature curve.
Little is known about the cause of pain in dysmenorrhoea, but it has been shown that it may be associated with strong contractions in over-excitable uterine musculature. Ischaemia is probably an important underlying circulatory disturbance. With the exception of dysmenorrhoea in cases of uterine hypoplasia,

[83] *Lax, H.:* Geburtsh. u. Frauenhk. **1**, 681 (1939).
[84] *Kraatz, H.:* Dtsch. Gesd.wes. **12**, 765 (1957) (Review).
[85] *Neuweiler, W.:* Praxis **41**, 1 (1952).

there is no particular endocrine pattern in this disorder. However, the results of hormone therapy in cases with dysmenorrhoea justify this method of treatment. One must, however, reckon with a proportion of failures. Membranous dysmenorrhoea, a condition in which the endometrium (down to the basal layer) is shed and expelled as one piece by painful uterine contractions, is a particularly distressing disorder[86, 87]. It is interesting that the hormonal suppresion of ovulation eliminates dysmenorrhoea without inhibiting bleeding[88].

**Treatment:**

1. The treatment of dysmenorrhoea with uterine hypoplasia:

a) Immediately following a menstrual period, oestradiol benzoate 5 mg. on alternate days x 5[89], or two tablets of Progynon C (Primogyn C) daily for two weeks[90].

b) In severe cases, temporary suppression of menstrual periods by induction of a "pseudopregnancy" (figure 65).

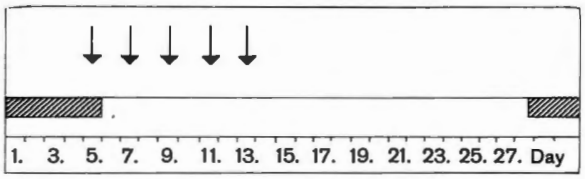



Figure 64. The treatment of dysmenorrhoea with oestradiol benzoate 5 mg. x 5 starting immediately after menstruation.

2. The treatment of dysmenorrhoea with a uterus of normal size:

a) Temporary suppression of ovulation with 1 tablet of Anovlar 21 or Gynovlar 21 from the 5th to 25th days of the cycle[88].

b) With hypermenorrhoea: Testoviron Depot (Primoteston Depot) x 1 between the 22nd and 25th days of the cycle.

Scheme 2a is suitable for the treatment of membranous dysmenorrhoea.

3. Dysmenorrhoea with symptoms characteristic of the premenstrual syndrome:

Three injections of Testoluton (Primofemin) between the 22nd and 28th days of the cycle[89a].

[86] *Giesen, W.:* Geburtsh. u. Frauenhk. 6, 104 (1944).
[87] *Greenblatt, H. R. B., & al.:* Amer. J. Obstetr. Gynec. 68, 835 (1954).
[88] *Peeters, F., & al.:* Med. Klin. 56, 1679 (1961).
[89] *Reichelt, O.:* Wien. med. Wschr. 103, 760 (1953).
[90] *Schuck, F.:* Amer. J. Obstetr. Gynec. 62, 559 (1951).
[89a] *Ufer, J.:* Geburtsh. u. Frauenhk. 14, 723 (1954).

**i) Premenstrual Syndrome[90a]**

Headaches, irritability, premenstrual mastodynia and pain due to pelvic congestion are symptoms which are commonly reported in the last few days before the onset of a menstrual period. In addition, it is well known that illnesses such as migraine, epilepsy[91] or gastro-intestinal disturbances, all of which have no obvious relation to ovarian function, may exacerbate in the premenstrual phase. The premenstrual syndrome usually occurs in women with a biphasic temperature curve.

*Pathogenesis.* In spite of many investigations, the pathology of the premenstrual syndrome has not, as yet, been adequately explained. Many observations lend support to the idea that there is a disturbance of hormone balance with an excess of oestrogens[92, 93] in the days preceding menstruation. At any rate, clinically and in experimental animals, it is possible to produce water and salt retention, mastodynia and other changes characteristic of the premenstrual syndrome by injecting oestrogens at the relevant time.

The nature of the symptoms suggests that the autonomic nervous system plays an important role in their genesis. In a few isolated cases, there may be disturbed liver function. A delayed or inadequate metabolism of oestrogens may cause a change in hormonal balance (the hepatogenic hyper-follicular state) with resulting premenstrual symptoms. In addition to the endocrine factors indicated, it is likely that dysfunction of the nervous system, as in women at the climateric, is of aetiological importance[95].

**Treatment:**

1. Two tablets of Primolut N daily from the 20th to 26th days of the cycle.

2. One ampoule of Testoluton (Primofemin) x 2 to 3 in the last ten days of the cycle[96].

Further measures: Treatment relevant to liver disease. Premenstrual fluid restriction. Prescription of diuretics and sedatives.

[90a] *Frank, R. T.:* Arch. Neurol. Psychiatr. 26, 1053 (1931).
[91] *Tewes, H.:* Ärztl. Wschr. 8, 252 (1953).
[92] *Narik, G., & Rockenschaub, A.:* Zbl. Gynäk. 73, 1607 (1951).
[93] *Ufer, J.:* Zbl. Gynäk. 74, 535 (1952).
[94] *Thorn, G. W., & Nelson, K. R.:* Endocrinology 22, 155 (1938).
[95] *Hauser, G., & al.:* Schweiz. med. Wschr. 89, 870 (1959).
[96] *Gilbert-Dreyfus, Z.:* Med. frç., Paris 25, 47 (1950).

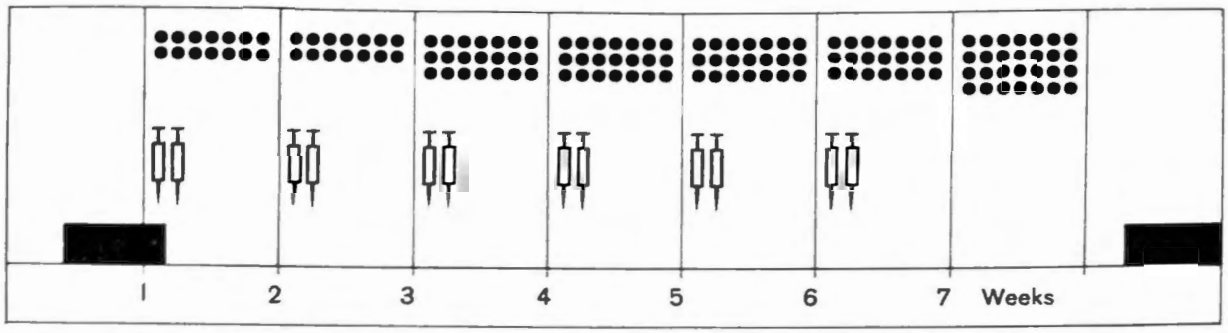



Figure 65. Treatment of uterine hypoplasia with Primolut N 10—20 mg. daily and Progynon Depot (Primogyn Depot) 20 mg. over a period of 7 weeks.

## II. Hypoplasia of the Genital Tract

Hypoplasia of the genital tract organs, particularly the uterus, may go hand in hand with generally deficient body development of constitutional origin. On the other hand, considerable degrees of hypoplasia may be found in otherwise normally developed people.

With deficient ovarian function (primary amenorrhoea, ovarian dysgenesis) the lack of uterine development betokens inadequate sex hormone production (page 28). If, however, general development is of the normal female type and there is cyclical menstruation, hypoplasia of the uterus must be interpreted as a sign of intrinsic deficiency. The different causes of uterine hypoplasia explain why the degree of uterine growth which can be achieved by hormone therapy is very variable[97].

Many disorders such as amenorrhoea, dysmenorrhoea, hypo- or hypermenorrhoea, disturbances of menstrual rhythm, infertility and repeated spontaneous abortion may accompany genital tract hypoplasia.

For the patient, the most important thing is that her symptoms should be alleviated. Although there is no agreed treatment for uterine hypoplasia, hormone therapy in young women with this manifestation is primarily aimed at increasing the degree of genital tract development.

The size of the uterus—its length is normally 7 to 9 cm.—is best measured by means of a uterine sound and the effect of treatment is also best judged in this way. If uterine malformation is suspected a hystero-salpingogram is indicated. The size of the uterus tends to regress in the months after discontinuing successful hormone therapy[98].

[97] *Clauberg, C.:* Zschr. Geburtsh. **107**, 331 (1934).

*Possible Methods of Treatment:*

Uterine growth is most markedly stimulated by oestrogens. There is evidence to suggest that the addition of progestogens in correct proportions has a synergistic effect on myometrial growth. Therapy should be adjusted accordingly. It can be cyclical or continuous, the latter resulting in "pseudo-pregnancy".

*The Principle Underlying Pseudo-pregnancy*

Treatment with oestrogens and progestogens in increasing doses mimics the hormone secretion pattern of pregnancy[98, 99]. Sex hormones cause uterine enlargement by means of their peripheral action and yet they depress the hypothalamic-anterior pituitary system by means of their central effect. Thus, the ovaries enter a resting phase. Ovulation and menstruation do not occur during treatment.

Pseudo-pregnancy not only makes the uterus larger and softer but is also accompanied by development of female secondary sex characteristics[100].

After treatment is discontinued (incidentally, progestogens only are given during the last week) moderately severe bleeding occurs. The first subsequent normal period can be expected after a further 6 weeks.

The chances of pregnancy appear to be increased in the month following treatment, probably as a result of a 'rebound effect' from a hypothalamic-anterior pituitary axis rendered somewhat sensitive by high levels of sex hormones[98a, 98b]. The rebound may also be responsible for remissions of menstrual disturbances, always desirable in a patient complaining of infertility.

[98] *Ufer, J.:* Acta endocr. **26**, 353 (1957).

[98a] *Buschbeck, H.:* Medizinische **1957**, 1523.

[98b] *Hohlweg, W.:* Med. Mitteilungen (Schering) **6**, 9 (1934).

[99] *Kaiser, R.:* Dtsch. med. Wschr. **81**, 744 (1956); Geburtsh. u. Frauenhk. **19**, 593 (1959).

[100] *Ufer, J.:* Münch. med. Wschr. **103**, 1928 (1961).

Table 19. *Different Types of Intersex* (*Prader, A.* and *Töndury, G.*)

| | Familial incidence* | Chromosomal sex | Gonadal sex | External genitalia | position of gonads |
|---|---|---|---|---|---|
| Female pseudo-hermaphrodite (adreno-genital syndrome) | G | ♀ | ♀ | intersexual | abdominal |
| Female pseudo-hermaphrodite with normal adrenal function. (Here the abnormality is produced by a congenital androgen-producing tumour or by maternal testosterone therapy in early pregnancy.) | — | ♀ | ♀ | intersexual | abdominal |
| Male pseudo-hermaphrodite with equivocal external genitalia (due to congenital testicular insufficiency). | GV | ♂ | ♂ | intersexual or male | variable |
| Testicular dysgenesis (congenital, almost complete testicular failure) | G? | ♂ | — | female | abdominal |
| Testicular feminization | GV | ♂ | ♂ | female | variable, usually inguinal |
| True hermaphroditism | ? | ♀ or ♂ | ♂ + | variable, usually intersexual | variable |
| Klinefelter Syndrome | G? | ♀ | ♂ | male | scrotal |

*G Affected siblings; V Affected distant relatives; ** Information gained by passing a uterine sound, X-rays, endoscopy

**Suggestions for Treatment:**

1. Cyclical therapy. At the end of a menstrual period, Progynon Depot (Primogyn Depot) 10 mg. is given and repeated 2 weeks later in combination with Proluton Depot (Primolut Depot) 250 mg.
Repetition of cyclical regime for several months.

2. Creation of a "pseudo-pregnancy"[98–100] without menstruation. Injections of Progynon Depot (Primogyn Depot) 10 to 20 mg. at weekly intervals x 6 to 7. Simultaneous treatment with Primolut N tablets, 10 mg. daily for the first 2 weeks, then 15 mg. daily and finally 20 mg. daily starting in the 7th or 8th week of therapy (figure 65). The progestogens should be continued for a week longer than the oestrogens[100].

3. An injection of 10 to 20 mg. of a crystalline suspension of oestradiol[101] into the uterine cavity or musculature every 4 to 6 weeks. If the vagina is particularly poorly developed, oestrogen pessaries can be tried.

The artificial vagina created by plastic surgical means shows a marked tendency to shrink. The regular use of vaginal dilators and oestrogen therapy are worth while and successful measures in such patients[102].

## III. Intersexual States (Table 19)

*Definition.* An intersexual state exists in patients where general appearances, genital tract development and the sex chromosome constitution are contradictory[103].

[101] *Husslein, H., & Gitsch, E.:* Zbl. Gynäk. **74**, 1582 (1952).
[102] *Ripman, H.:* Lancet **6711**, 744 (1952).
[103] *Prader, A., & Töndury, G.*, from Labhart, A.: Klinik der inneren Sekretion, Berlin 1957, 645.

from *Labhart, A.*: Klinik der inneren Sekretion, Berlin 1957, S. 653)

| Findings on rectal examination | Vagina** | Secondary sex characteristics | Menstruation | Excretion of GH a. 17 KS | Particular features |
|---|---|---|---|---|---|
| uterus<br>uterus | normal, sometimes opens into a uro-genital sinus | male | — | ↑↑↑ ↓↓ | generally precocious development; virilization |
| | | female | + | n? n? | |
| variable | variable | variable | — | n ↑ | |
| uterus | normal | barely developed | — | ↓ ↑ | dwarfism, pterygium colli etc. |
| no uterus | short and ends blindly | female | — | n ↑ | no pubic hair, herniae |
| variable | variable | variable | variable | n/↓ n/↑ | |
| prostate | absent | male + with gynaecomastia | — | ↓ ↑ | small testes |

and speculum examination; + present; — not present; n normal; ↑ raised; ↓ diminished.

If the gonads or chromosome constitution are male, while general appearances and the genitalia are female, one speaks of a male pseudo-hermaphrodite, while in female pseudo-hermaphrodites the findings are reversed. A diagnosis of intersex can, therefore, not be made on external appearances. True hermaphroditism is a rare condition where the gonad is an 'ovo-testis' [104].

Strictly speaking, the definition given demands that women with hirsutism or men with gynaecomastia should be regarded as examples of intersexuality.

*Diagnosis.* General and pelvic examination are rarely sufficient for exact diagnosis and classification. In addition to vaginal and rectal examinations, endoscopy is important.

Of various hormone excretion studies, the measurement of 17-ketosteroids in urine is of the greatest importance, particularly in women with signs of virilism (pages 64, 84).

The study of chromosomes by blood culture or by sex chromatin determinations according to the methods of *Barr*[105–107] (page 60), provides exact evidence about the pathogenesis of any intersexual state.

It has, for example, been shown that some patients with a completely female phenotype are chromosomally-speaking males (the testicular feminization syndrome). Detailed study of the karyotype provides exact evidence concerning congenital malformations. A laparotomy for full genital tract appraisal and gonadal biopsy may be indicated if an exact diagnosis is required.

[104] *Overzier, C.*: Acta endocr. **20**, 63 (1955).

[105] *Moore, K. L., & Barr, M. L.*: Surg. Gyn. Obstetr. **96**, 641 (1953).

[106] *Ehrengut, W.*: Zschr. Kinderhk. **77**, 322 (1955).

[107] *Tolksdorf, M., & al.*: Ärztl. Wschr. **10**, 1029 (1955).

*Aetiology*. The chromosomal sex is determined as soon as male and female gametes fuse. In the first weeks of pregnancy, the gonads develop, followed by differentiation of the internal and external genitalia. Normally chromosomal, gonadal and genital tract sex are the same (page 25). With failure of gonadal development, a female genital tract always develops, perhaps in response to the effect of placental hormones[108]. This explains why individuals without gonads are registered as females at birth and are brought up as girls although their chromosome constitution is male (page 25).

Male differentiation of the genital tract only occurs in the presence of testes, which presumably start secreting androgens very early in embryonic life. If testicular development is deranged, an intersex develops (male pseudo-hermaphrodite). An unusual type of intersex is the 'testicular feminization syndrome'[109]. This arises when embryologically normal testes fail to influence genital tract differentiation by androgens.

It is due to a peripheral lack of sensitivity to androgens caused by an enzyme defect[109a]. If, on the other hand, excessive androgens, e.g. from abnormal adrenals, influence a female embryo, an intersexual state develops with a male phenotype in the presence of female gonads and sex chromosome constitution (pseudo-hermaphroditism — congenital adreno-genital syndrome, page 84). Excessive hair on the trunk and limbs is often due to ovarian disorder (see *Stein-Leventhal* syndrome, page 83). Often, constitutional factors may operate without any co-existent evidence of endocrine disease.

**Treatment:**

Because of the fundamental nature of the disturbance, the therapeutic possibilities in these cases are strictly limited. Whatever treatment is given depends on sex determination at birth and the individual's subsequent development. Gonadal or chromosomal sex which is at variance with mental and physical development must never be given over-riding im-

[108] *Jost, A.:* 3. Symposion d. Deutschen Gesellschaft f. Endokrinologie, 4./5. III. 1955, Springer-Verlag, Berlin 1956, 14.

[109] *McLean Morris, J., & Mahesh, V.:* Amer. J. Obstetr. Gynec. **87**, 731 (1963).

[109a] *Wilkins, L.:* Diagnosis and Treatment of endocrine Disorders in Childhood, Verlag C. Thomas, Springfield 1957.

Table 20. *The hormonal factors which play a role in reproduction*

(Modified *Nelson, W. C.:* Acta endocr., Suppl. **28**, 7 [1956])

| | |
|---|---|
| | ● Transport and formation of male gametes and seminal fluid |
| | A. Gametogenesis |
| | 1. Multiplication of spermatogonia |
| | 2. Reduction division of primary spermatocytes |
| FSH, ICSH and Androgens | 3. Formation of spermatozoa from spermatocytes |
| | 4. Liberation of sperms |
| | B. Sperm transport |
| | 1. Physiological maturation of sperms within the epididymis |
| | 2. From the testis to the spermatic cord |
| | C. Formation of seminal fluid |
| Androgens | 1. Secretion from the seminal vesicles |
| | 2. Prostatic secretion |
| | ● Formation and transport of female gametes and preparation of uterus for nidation |
| | A. Formation of gametes |
| FSH LTH | 1. Growth of ovarian follicle |
| | 2. Maturation of ova |
| | 3. Ovulation |
| | B. Transport of ova |
| | 1. Entry of egg into Fallopian tube |
| | 2. Transport of egg to uterus |
| Oestrogens Progesterone | C. Preparation of endometrium |
| | 1. Proliferative changes |
| | 2. Secretory changes |
| | ● Process of fertilization |
| | A. Transport of sperms through female genital tract |
| | 1. Passage of sperms from vagina to Fallopian tube |
| | 2. Maturation of sperms within female genital tract |
| | 3. Entry of sperm into egg and fusion of germ cell nuclei |
| | ● Nidation and early development of zygote and embryo |
| | A. Development of zygote |
| | 1. Division of fertilized egg |
| | 2. Formation of blastula |
| | 3. Formation of primary germ layers |
| HCG, Progesterone, Oestrogens | B. Nidation |
| | 1. Embedding of ovum |
| | 2. Early placental development. |

Table 21. *Tests for Ovulation*
(Amplified and modified) *Stimmel, B. F.:* Fertility and steril., 10, 91 [1959])

| Test | Degree of certainty | Clinical practicality | Timely diagnosis of ovulation | Repeated testing necessary |
|---|---|---|---|---|
| 1. Pregnancy | ++++ | (++++) | no | |
| 2. Mittelschmerz | ++ | ++ | no | |
| 3. Ovulatory bleeding | ++ | ++ | no | |
| 4. Measurement of waking temperature | +++L* | ++++ | no | yes, daily recordings |
| 5. Ruptured follicle or fresh corpus luteum observed at laparotomy or culdoscopy | ++++ | ++ | no | |
| 6. Cyclical changes in diameter of external os | ++ | +++ | yes | yes |
| 7. Volume of cervical mucus | ++ | +++ | yes | yes |
| 8. "Threadability" or Spinnbarkeit of cervical mucus | ++ | +++ | yes | yes |
| 9. Glucose in cervical secretion | + | ++ | yes | yes |
| 10. Premenstrual disappearance of fern pattern | ++ | +++ | no | |
| 11. Premenstrual endometrial biopsy | +++L* | +++ | no | |
| 12. "Luteal" change in vaginal epithelium | ++ | ++ | no | yes |
| 13. Increased gonadotrophin (mainly ICSH) secretion before and during ovulation | + | (+) | ? | yes |
| 14. Increased oestrogen excretion at the time of ovulation | + | (+) | yes | yes |
| 15. Premenstrual rise in pregnanediol excretion | +++L* | ++ | no | |

* Tests markes "L" are suitable for assessing the function of the corpus luteum.

portance in decisions concerning treatment directed at "sex change".

Hormone therapy is indicated in cases of adreno-genital syndrome (page 84) or in patients with ovarian agenesis or dysgenesis (page 70). Operative procedures (such as removal of hormone-producing tumours, vaginal plastic surgery, removal of an enlarged clitoris) will not be considered here.

In patients with constitutional virilization (page 85), where adrenal or ovarian dysfunction has been excluded, a case can be made out for long-term treatment with corticoids.

Dose: Prednisolone 10 mg. daily for several months.

## IV. Infertility

Infertility is established when pregnancy does not occur after two years of marriage with intercourse at regular and frequent intervals and no contraceptive measures[110]. Infertility is not a disease but a status for which there may be a number of reasons[111]. It is probable that endocrine disorders are more often responsible in women than is generally believed. Four distinct groups can be identified:

1. Infertility due to genital tract hypoplasia.
2. Infertility due to failure of ovarian function.
3. Infertility due to insufficiency of the corpus luteum.
4. Infertility due to repeated early abortion.

*Diagnosis:* A patient may belong to more than one of the above groups and careful diagnosis with accurate, even prolonged observation is therefore necessary. The most critical questions concern the occurrence and timing of

[110] *Grünberger, V.:* Geburtsh. u. Frauenhk. 15, 142 (1955).

[111] *Wenner, R.:* Grundriß der gynäkologischen Endokrinologie, Basel 1952, 259.

ovulation. It is often difficult to answer these, in spite of the many tests described for the detection of ovulation[112]. The accurate prediction of ovulation presents particular problems.

After organic disease has been excluded by gynaecological examination, both partners of an infertile marriage should be subjected to investigations which test the patency of the channels along which their respective germ cells must travel.

*Basal body temperature records* should be kept in order to provide information about ovarian function, the optimal time in the cycle for conception and the duration of the secretory phase of the menstrual cycle. These records should always be obtained before any active treatment for infertility begins. In many cases, they clearly indicate the exact timing of ovulation, the cause of infertility, the duration of the secretory phase of the cycle (a very critical factor) and the "fertile and infertile" days of the cycle[113]. Ovulation does not occur on the day the temperature rises but one to three days earlier, in most cases on the actual day on which the lowest temperature is recorded.

It seems that fertilization is unlikely after the thermal shift has occurred[114]. It is said that if the luteal phase of the cycle lasts less than 14 days, infertility is the invariable sequel. Nidation occurs 8 to 10 days after the ovum has been fertilized and is greatly hampered by too short an interval between ovulation and the onset of menstruation. If the "premenstrual" rise of temperature is prolonged and followed by bleeding, this probably means early abortion. The temperature rise in the premenstrual phase of the cycle is often so atypical as to make it impossible to be certain about ovulation. Ovulation may even occur during monophasic cycles[115]. It is thus desirable to employ more than one test for the diagnosis of ovulation and the assessment of corpus luteum function (table 21).

Premenstrual endometrial biopsy (page 55), provides information about endometrial status. Thin endometrium with scanty glands and not much in the way of secretory activity is not a good substrate for the fertilized egg. Absence of secretory change or transformation is evidence of failure of ovulation.

A third simple test which can be done without laboratory facilities is a serial study of the cervix and its secretions[116] (page 55).

| | Quantity ▨ | Degree of Transparency ▯ | Size of the Cervical os ▮ |
|---|---|---|---|
| 4 | very abundant cascade | clear | gaping |
| 3 | abundant | partly becoming unclear | open |
| 2 | moderate | turbid | half open |
| 1 | little or missing | opaque | closed |

Fig. 66. Scheme which serves to explain fig. 67: The recording of changes in the cervix.

This has the advantage, not shared by basal body temperature records, of providing evidence about impending follicular rupture during the proliferative phase of the cycle[117,118]. The volume of cervical secretions begins to increase on the 8th day of the cycle. In a smear, moderate "ferning" is seen. On the 12th day the external os gapes somewhat, particularly in nulliparous subjects. The cervical secretion is clear, copious and "threadable". Subsequently, and at about the time of ovulation, clear mucus "pours" from the cervix. The "ferning pattern" becomes marked. The cervical mucus develops "Spinnbarkeit" which means that it can be drawn out to a length of 8 cm. between two platinum loops. Its characteristics are, in fact, such that its sperm penetrability is maximal at this time—the basis of a positive *Sims-Huhner* test.

The *Miller-Kurzrock* test answers questions about possible differences in the sperm penetrability of cervical mucus when tested with husband and with donor semen[119].

[112] *Sillo-Seidl, G.:* Zbl. Gynäk. **83**, 1898 (1961).

[113] *Knaus, H.:* Die periodische Fruchtbarkeit und Unfruchtbarkeit des Weibes, Wien 1953.

[114] *Döring, G. K.:* Geburtsh. u. Frauenhk. **10**, 515 (1950).

[115] *Horsky, J., & Marsalek:* Gynaecologia **129**, 396 (1950).

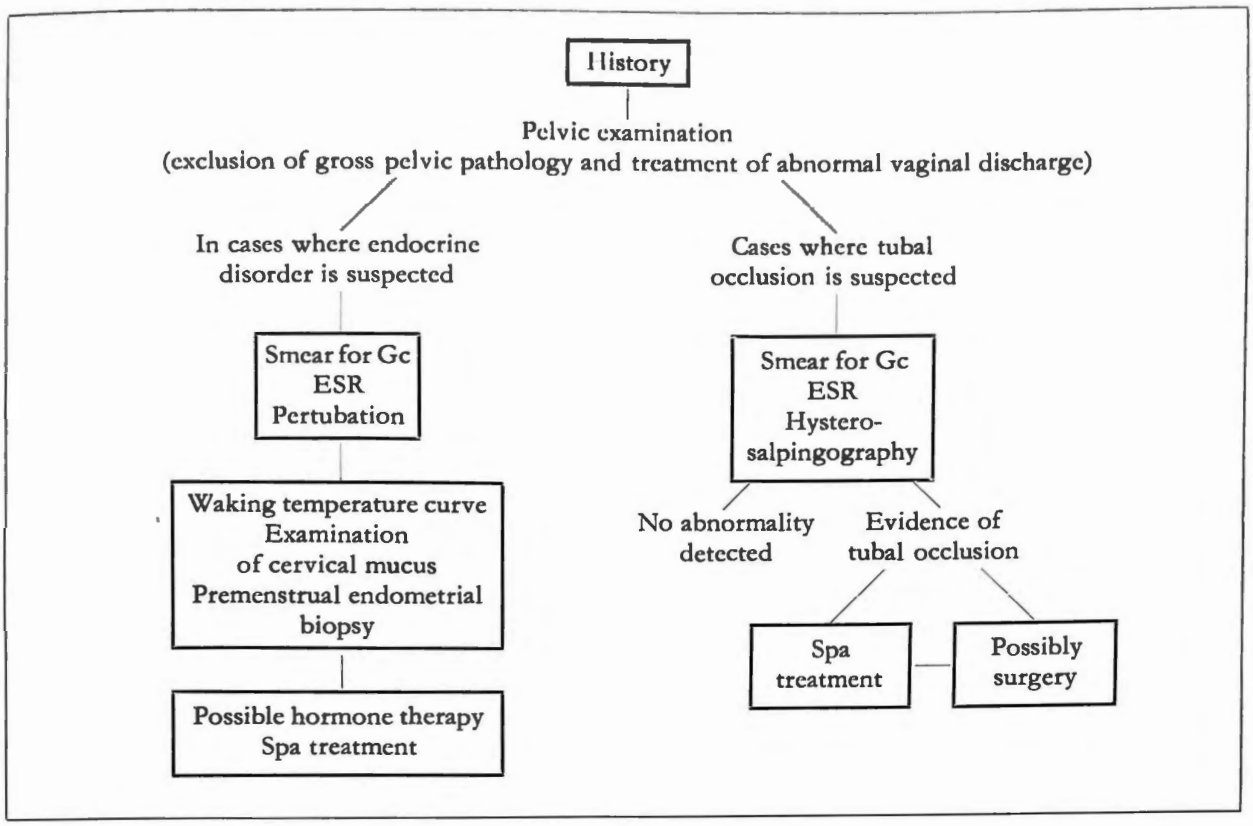
[116] *Shettles, L. B.:* Klinische Fortschritte in der Gynäkologie, Wien 1954.

[117] *Kühnelt, H. J.:* Geburtsh. u. Frauenhk. **16**, 651 (1956).

[118] *Igarashi, M., & al.:* Amer. J. Obstetr. Gynec. **73**, 1294 (1957).

[119] *Leeb, H.:* Beiträge z. Steril. u. Fertil., Enke-Verlag, Stuttgart 1960, 31.

Table 22. *Management by female infertility*




Between the 18th and 20th days of the cycle, after ovulation and during the secretory phase, the amount of cervical mucus diminishes considerably and the "fern pattern" is only rarely seen. At this time, it is also not possible to draw out the cervical mucus between 2 platinum loops.

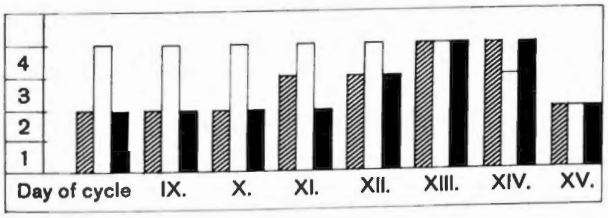



Figure 67. State of cervix and cervical mucus between the 8th and 15th days of a biphasic, 27-day cycle (see figure 66).

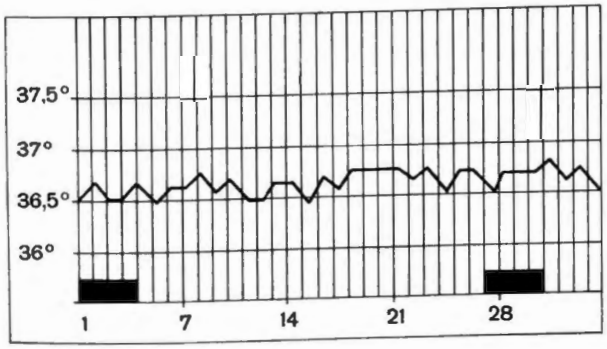



Figure 68. Monophasic, anovulatory cycle.

In the absence of ovulation, none of these changes are seen. Repeated observation of the cervix by speculum examination can, in experienced hands, provide enough information to decide whether or not ovulation is occurring. This is shown in the schemes presented in figures 66 and 67[120].

More complicated methods of detecting ovulation are vaginal smears (which measure oestrogen activity, see page 55) and hormone assays, pregnanediol estimations being the most important.

*Treatment:*

General Remarks.

After initial history-taking, examinations and investigations, patients should always be warned that treatment may be long, tedious and subject to frequent changes or adjustments. In addition it is necessary to make arrangements for investigating the male partner's fertility. Apart from special measures, a change of climate, a period of separation between husband and wife or treatment in a spa etc. may be advisable.

[120] *Rauscher, H.:* Geburtsh. u. Frauenhk. **16**, 900 (1956).

### a) Infertility with Genital Tract Hypoplasia

The likelihood of conception depends on the age of the patient and the size of the uterus. If the latter is not too small, the outlook is favourable. Cases in which ova are not being released carry a poorer prognosis. For suggestions concerning treatment see page 82 and 97.

### b) Infertility due to Failure of Ovulation

(see page 91)

A diagnosis of "infertility due to failure of ovulation" demands that at least 3 out of 6 observed cycles are anovulatory.

Treatment depends on aetiological factors[121]. General physical measures or an improvement in living conditions may be indicated.

Sex steroids or gonadotrophic substances may be used as hormone therapy. If there is evidence of virilization, treatment with glucocorticoids may be indicated.

The prognosis in cases of infertility due to failure of ovulation depends on a number of things. The state of the ovaries is of dominant importance. If organic changes, such as exhaustion of the supply of Graafian follicles (early climacterium), or incomplete ovarian development (hypogenesis) are to hand, a biphasic menstrual cycle can, at best, only be achieved as a transient improvement.

#### Suggestions for Treatment:

Treatment with gonadotrophic hormones[122] (figure 69)

1. Anteron (Primantron) 1000 IU × 3 between the 5th and 9th days of the cycle followed by:
Primogonyl[123, 124] 1000 to 5000 IU intramuscularly × 3 on the 9th, 11th and 13th days of a cycle. Once ovulation has occurred, Primogonyl can be discontinued.

2. Treatment with sex hormones:
Progynon Depot (Primogyn Depot) 10 mg. on the 6th and 18th days of the cycle.
Proluton Depot (Primolut Depot) 250 mg. on the 18th day for several cycles.

3. Treatment with glucocorticoids (in cases of virilism, see page 85) prednisolone tablets, 10 mg. daily for several months.

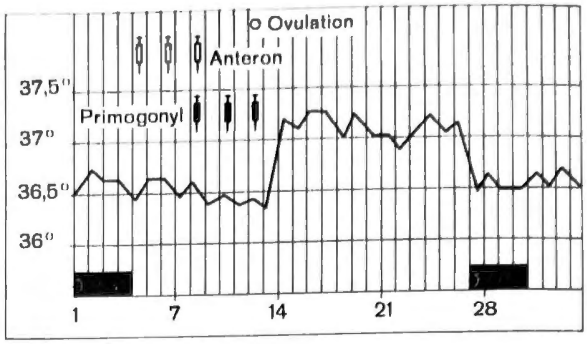



Figure 69. Suggested method of using gonadotrophins for the induction of ovulation (Anteron [Primantron] = PMS, Primogonyl = HCG).

### c) Infertility due to Corpus Luteum Insufficiency (abbreviated menstrual cycle)

Repeated pregnanediol estimations, basal body temperature records and premenstrual endometrial biopsy[125] indicate whether the formation of progesterone by the corpus luteum is sufficient to allow nidation of the fertilized egg. Clinically, polymenorrhoea is frequently a symptom of insufficient corpus luteum function. Combined progestogen and oestrogen therapy can delay the onset of menstruation and enhance endometrial secretory activity. In this way, the fertilized egg is given time to implant normally in the uterine endometrium. The nutrient materials necessary for normal development of the fertilized egg can be found in endometrium whose secretory activity has been enhanced by progestogen therapy.

#### Suggestions for Treatment:

One ampoule of Primosiston on the 16th day of the cycle.

### d) Infertility due to Early Abortion

Many early abortions are due to blighted ova or moles. The ovum may die so early that the abortion passes unnoticed and is thought to be a delayed menstrual period. Implantation of the fertilized egg is a complex process dependent on a number of maternal and biological factors. Genetic factors (for which there is no treatment) as well as faulty nidation and deficient decidual changes in the endometrium may cause death of the fertilized ovum.

It is not surprising that the quality of secretory and decidual changes are of great significance to the embryo, which relies on these

[121] Review: International Congress of Fertility and Sterility. Naples (1956), Amsterdam (1959).
[122] *Béclère, C.:* Sem. hôp. **39**, 2901 (1963).
[123] *Rydberg, E., & Madsen, V.:* Acta obstetr. gynec. Scand. **28**, 386 (1949).
[124] *Will, I.:* Med. Klin. **50**, 1859 (1955).
[125] *Gillam, J. S.:* Fertility and steril. **6**, 18 (1955).

sources for its considerable oxygen consumption and other nutritional requirements[126].

In cases where the post-ovulatory elevation of basal temperature has lasted more than two weeks and an increase in pregnanediol excretion has been observed, "delayed menstruation" probably means early abortion.

The chances that the nutritional requirements of the embryo are satisfied during nidation can be improved by the prophylactic use of oestrogenic and progestational drugs starting shortly after ovulation[127–129].

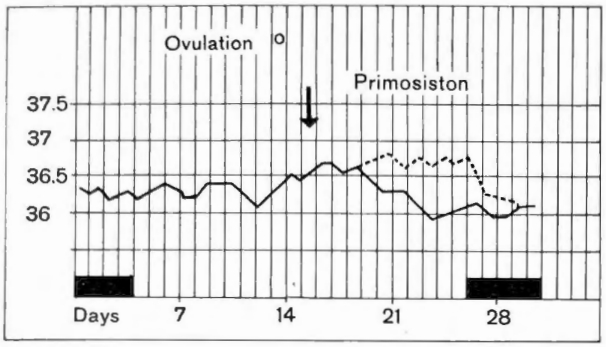



Figure 70. Waking temperature with corpus luteum insufficiency. Temperature curve after treatment with 1 ampoule of Primosiston, on the 16th day of the cycle.

**Suggestions for Treatment:**

Two or three days after coitus at the estimated time of ovulation, weekly injections of Progynon Depot (Primogyn Depot) 10 mg. and Proluton Depot (Primolut Depot) 250 mg. should be commenced.

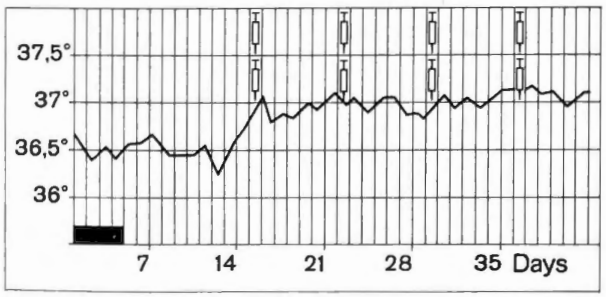



Figure 71. The use of Proluton Depot (Primolut Depot) 250 mg. and Progynon Depot (Primogyn Depot) 10 mg. in a case with a previous history of early miscarriages. The temperature curve suggests pregnancy.

By taking the waking temperature it is possible to detect pregnancy very early as Proluton Depot (Primolut Depot) itself has no thermogenic effect. If the basal temperature starts to fall, further treatment is pointless (see figures 71 and 72).

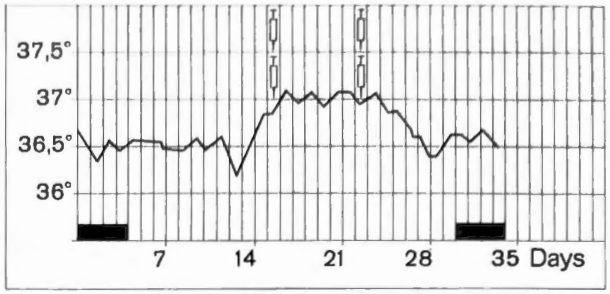



Figure 72. The same treatment as in figure 71. In spite of Proluton Depot (Primolut Depot) and Progynon Depot (Primogyn Depot) the waking temperature falls on the 28th day and further treatment is pointless. Menstruation is somewhat delayed.

## V. Hormones for Contraception

Although *Pincus, Rock and co-workers*[130–132] only introduced modern oral contraceptive therapy in the mid-fifties, it has long been known that conception hardly ever occurred during treatment with oestrogens and progesterone. Oral contraceptive therapy is based on the fundamental and classical observation that sex hormones have a centrally depressant and peripherally stimulant action. The American workers, using skillful combinations of progestogen and oestrogen, were able to suppress follicular maturation and ovulation and still obtain regular monthly bleeding of the "pseudo-menstrual", hormone-withdrawal type.

### *Method of Action*

As in early pregnancy, oestrogens and progestogens have an inhibitory effect on hypothalamic/anterior pituitary function which leads to diminished release of gonadotrophins from the anterior pituitary[133] (figure 73). This inhibition deprives the ovary of the physiological impulses which evoke follicular matura-

[126] *Hertig, A. T., & Rock, J.:* Amer. J. Anatom. **98**, 435 (1956).
[127] *Brown, R. Chr.:* Brit. Med. J. **4584**, 857 (1948).
[128] *Hughes, E. C., et al.:* Int. Gyn. Kongr. 1954, 715.
[129] *Käser, O.:* Schweiz. med. Wschr. **91**, 352 (1961).
[130] *Pincus, G.:* Acta endocr. **28**, 18 (1956).
[131] *Rock, J., et al.:* Recent Progr. Hormone Res. **13**, 323 (1957).
[132] *Rock, J., et al.:* Science **124**, 3227 (1956).
[133] *Buchholz, R., et al.:* Geburtsh. u. Frauenhk. **22**, 923 (1962).

tion and ovulation. As in pregnancy, the ovaries enter a resting state. Oestrogen determinations in urine have shown that the endocrine function of the ovary is not entirely dormant during treatment. About one third of the physiological amounts are formed. Withdrawal bleeding occurs two to three days after discontinuing treatment. Subsequently, treatment must be started again if contraceptive protection is to be maintained.

After discontinuing therapy, a biphasic cycle soon reappears and in some cases, a prolonged follicular phase may be seen. Conceptions frequently occur after the end of treatment—this has led to the idea of a *rebound* phenomenon.

At present, two methods of treatment are employed.

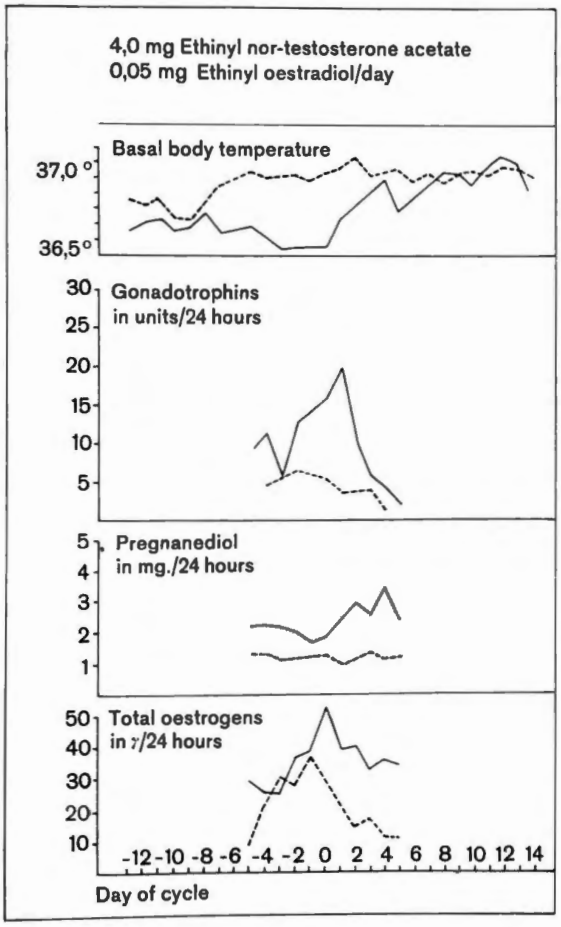



Figure 73. Basal body temperature, pregnanediol, total oestrogen (= oestrone+oestriol+oestradiol 17β) and gonadotrophin excretion in a group of 7 mature women without treatment and while taking norethisterone acetate 4 mg. + ethinyl oestradiol 0.05 mg./day from the 5th to 24th days of the cycle.
—— without treatment ------ during treatment
(*Buchholz, R., et al.:* Geburtsh. u. Frauenhk. **22**, 923 [1962])

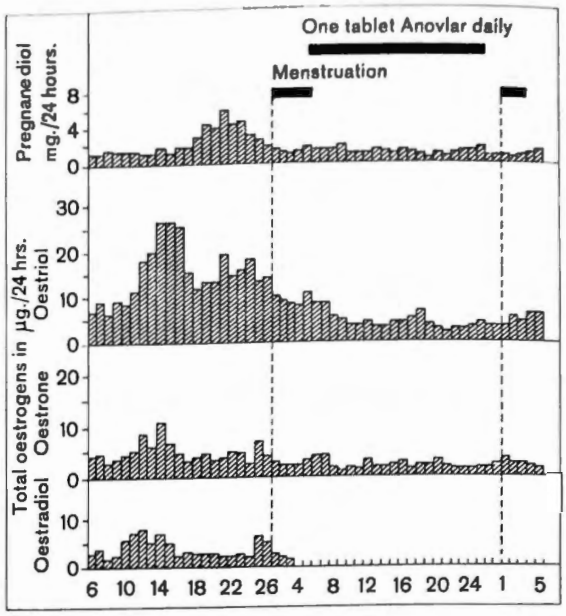



Figure 74. Oestrogen and pregnanediol excretion pattern before and during treatment with Anovlar. (*Shearman, R. P.:* Lancet **7274**, 197 [1963])

## I. Oestrogen-progestogen therapy from the 5th to 25th days of the menstrual cycle

During these days, one tablet of Anovlar (or some other preparation) is taken daily. This leads to a decrease in gonadotrophin excretion[133] and to early secretory transformation of the endometrium. In the last ten days of treatment the endometrial glands tend to regress while the stroma becomes oedematous[134]. Two to three days after interrupting treatment, slight menstrual-type withdrawal bleeding occurs. By starting oestrogen-progestogen therapy early in the cycle, physiochemical changes characteristic of the luteal phase are seen in the cervical mucus. The "ferning pattern" disappears (page 55). This makes conditions unfavourable for migration of sperms through the cervical canal because they are unable to penetrate cervical mucus. Study of the endometrium and cervix during treatment shows that, apart from preventing follicular ripening and rupture, oral contraceptives have at least two further methods of action which contribute to their effectiveness and safety. Three-fold security is thus available:

Absolute protection due to inhibition of ovulation.

Relative protection due to disturbance of the secretory changes normally seen in the second half of the cycle.

Relative protection due to changes in cervical mucus.

| *Advantages of oral contraceptive therapy (Method I)*[135, 136]: |
|---|
| From the second cycle of treatment, one hundred per cent protection against conception. Ovulation may not be suppressed during the first treatment cycle, particularly in women who tend to ovulate early[137]. |
| There are no *absolute* contraindications to combined oestrogen-progestogen therapy[141]. A history of previous phlebothromboses or chronic liver disease constitute only *relative* contra-indications to treatment as there is no certain evidence that it leads to recurrences of the conditions mentioned. Clotting mechanisms are only slightly affected by treatment with oral contraceptives[138–140]. |
| There is no *irreversible* damage to the hypothalamic/anterior pituitary axis or to the ovaries[142]. There are many reports of pregnancy[137] and biphasic cycles[144] even after years of treatment. |
| As with women who have had many children, the menopause is not delayed if oral contraceptives are taken for longer periods of time. |
| Atypical proliferative changes in the endometrium indicating carcinomatous metaplasia *do not occur*. The proliferative activity of the endometrium is less than during normal menstrual cycles. |
| The adrenals are only minimally affected, although the excretion of corticoids diminishes. There is a rise in the level of plasma corticoids[139]. |
| Many disorders which tend to remit during pregnancy are favourably influenced by oral contraceptive therapy. Migraine and eczema are among these conditions. |

*Disadvantages of oral contraceptive therapy (Method I)*[143]:

Although a number of somewhat unpleasant side-effects do occur[130], on the whole they are of no particular significance. At the onset of therapy, they occur in some 30 per cent of women treated. After longer spells of treatment, this figure is considerably smaller.

The following side effects may occur:

| Mid-cycle bleeding which is usually slight and may require a supplement of Progynon C (Primogyn C) one tablet daily. |
|---|
| Heavy "break-through" bleeding which necessitates interruption of a course of treatment. The next lot of tablets can be started after a lapse of 8 days. |
| Amenorrhoea which is in fact a failure of hormone withdrawal type "pseudo-menstruation". If this occurs after the first cycle of treatment, pregnancy must be excluded by examination and by immunological pregnancy tests before hormone therapy can continue. If amenorrhoea occurs repeatedly "sequential therapy" should be tried. |
| Headaches, nausea and premenstrual tension are symptoms which usually disappear as treatment continues. |
| Weight increase is only seldom seen. It is never troublesome when treatment has been administered for some length of time. In mothers who are breast feeding there is often a reduction in lactation. |
| Illnesses such as epilepsy, otosclerosis and neurological disorders, which tend to get worse during pregnancy are often adversely influenced by oral contraceptive therapy. |
| Some claim a reduction in libido, while others have reported increases. There is hardly any direct effect on sex life. |

[134] *Maqueo, M., et al.:* Amer. J. Obstetr. Gynec. **85**, 427 (1963).
[135] *Kaiser, R.:* Dtsch. Med. Wschr. **88**, 2325 (1963).
[136] *Kirchhoff, H., & Haller, J.:* Therapiewoche **14**, 33 (1964).
[137] *Peeters, F., et al.:* Bayr. österr. schweiz. Gyn. Tagung 1963, Luzern.
[138] F. D. C. Reports August 5, 1963.
[139] *Wallach, E., et al.:* Amer. J. Obstetr. & Gynec. **87**, 991 (1963).
[140] *Ludwig, H.:* Bayr. österr. schweiz. Gyn.-Tagung, Luzern 1963.
[141] *Peeters, F., et al.:* Scalpel **114**, 1117 (1961).
[142] *Peeters, F., et al.:* Med. Klin. **56**, 1679 (1961).
[143] *Richter, R. H. H., & Schreiner, W. E.:* Therap. Umschau **20**, 489 (1963).
[144] *Loraine, J. A., et al.:* Lancet **7314**, 902 (1963).

*Duration of treatment:*

It is not yet certain how long oral contraceptive therapy can continue without harmful effect. The fact that treatment, rather than being continuous, is intermittent seems to be important in preserving a potentially normal endocrine status. Many observers have reported that after 2 to 5 years of treatment, ovaries again become fully functional after one or two cycles without drugs[137, 144]. The endometrium also returns to normal cyclical changes. Some authorities believe that an increased rate of conception[145] in the first months after treatment represents a "rebound phenomenon". These observations lend support to the view that treatment lasting up to 4 years need cause no anxieties[138]. However, as a precautionary measure, it might be wise to discontinue treatment in young women after about a year. If the basal temperature curve then returns to a biphasic pattern, it is reasonable to embark on further therapy.
After delivery, oral contraceptives should be withheld until a regular menstrual cycle is re-established. Under no circumstances should therapy begin before the first post-partum menstrual loss has occurred.

## II. Sequential Therapy[146, 135]

Each treatment consists of two phases. From the 5th to the 18th day of a cycle, oestrogens alone are given at doses which are known to suppress ovulation with certainty. Subsequently, an oestrogen-progestogen combination is given for a further 7 days as in paragraph I.

*Advantages of sequential therapy:*

1. It more closely resembles the physiological menstrual pattern.

2. Treatment is less costly.

*Disadvantages:*

This type of treatment has not had such thorough trial. More pregnancies occur during sequential therapy than with Pincus's method of treatment. The success of sequential therapy depends on the suppression of ovulation (there is no three-fold security as with scheme I). The same side effects are seen as with scheme I.

*Application to gynaecological disorders*

Treatment with oestrogens and progestogens which resembles that used for oral contraceptive purpose, can be successfully applied to patients with gynaecological disorders.

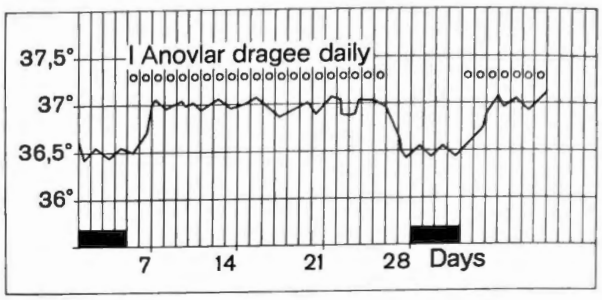



Figure 75. Waking temperature curve during treatment with Anovlar from the 5th to 25th days of a cycle.

These include dysmenorrhoea (page 95), endometriosis (page 118), hypermenorrhoea and polymenorrhoea. The method of treatment must be explained to the patient in detail.

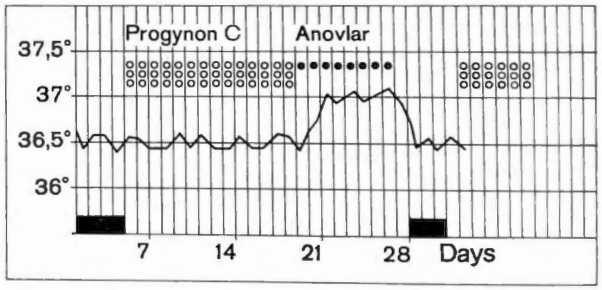



Figure 76. Waking temperature curve during treatment with 1 tablet Progynon C (Primogyn C) three times daily from days 5—18 and 1 dragee of Anovlar daily from days 19—26.

### Suggestions for Treatment:

I. One tablet of Anovlar 21 or Gynovlar 21 from the 5th to the 25th day of a menstrual cycle. After an interval of one week without therapy, treatment is started again on the same day of the week as in the previous cycle.

II. Progynon C (Primogyn C) three tablets daily from the 5th to the 18th day of the menstrual cycle.

One tablet of Anovlar 21 or Gynovlar 21 daily from the 19th to 26th day of the cycle.

145 *Goldzieher, J. W.:* Amer. J. obstetr. & Gynec. 84, 1474 (1962).

146 *Goldzieher, J. W., et al.:* 7. Int. Conf. Plann. Parenthood (1963).

## VI. Frigidity

A woman's sexual drive depends primarily on her attitude to her male partner and on psychological factors. There is, however, some evidence to suggest a limited relationship between libido and ovarian function[147]: individuals with infantilism due to absent or faulty ovarian development are always frigid. The same often applies to women with deficient genital tract development. Oestrogens may cause an increase in the size of female sex organs. As a result, normal sex life may be achieved. By contrast, bilateral oophorectomy does not lead to frigidity in women with normal libido.

Normal women get mentally depressed on high doses of oestrogens while androgens are stimulant and make them euphoric[148].

High doses of testosterone, sometimes used in the treatment of breast carcinoma, quite often cause pathological increases of sex drive[149]. In addition, clitoral enlargement may be observed.

Early hopes about the usefulness of oestrogens with these disorders were based on the results of animal experiments and have only been realised to a very limited degree. Oestrogens probably only improve the sex life of patients with a hypoplastic genital tract by provoking menstrual blood loss.

The therapeutic use of testosterone is also often misguided if applied to circumstances where the basic error lies in a patient's psychology or in her environment. Testosterone preparations should not be used to increase libido in women who show even the slightest signs of virilization. It is said that normally developed women with a delicate skin and premenstrual symptoms often complain about a lack of libido. In them, treatment with testosterone may have a beneficial effect[150, 151]. The dosage of androgens should be so adjusted as not to cause menstrual disturbance.

It seems hardly necessary to stress that hormone therapy should not be prescribed until a genital tract cause for frigidity such as prolapse, cervical discharge, vaginitis or parametritis has been excluded. Women with libido who do not experience orgasm carry a relatively favourable prognosis. Psychiatric treatment may be greatly facilitated or speeded by simultaneous administration of androgens[152].

**Suggestions for Treatment:**

1. With hypoplasia of the genital tract: combined oestrogen-progestogen therapy (page 97).
2. With normal genital tract development: androgens in the form of one tablet of Testoviron (Primoteston) (methyl testosterone) 5 mg. daily.
3. With premenstrual symptoms: androgen therapy in the form of Testoviron Depot (Primoteston Depot) 100 mg. on about the 20th day of the cycle.

## VII. Disorders of Pregnancy and the Puerperium

### a) Abortion

*Pathogenesis.* Countless processes are involved in fertilization, nidation and early development of the zygote (page 25). They are only briefly summarized below[153]:

| |
|---|
| The zygote must be formed by fusion of two healthy, normal and compatible gametes. |
| Nidation must occur under physiological conditions which allow normal development and function of trophoblastic tissue. |
| The delicate hormone balance of pregnancy must be maintained. |
| The placenta must be able to fulfill its many roles. |
| The uterus must provide a favourable environment for nutrition of the fertilized egg for a sufficient length of time. |
| The mental state of the prospective mother must be devoid of tension. |

147 *Rabach, J., et al.:* Endokrinologie **45**, 52 (1963).
148 *Bleuler, M., & Zublin, W.:* Wien. med. Wschr. **100**, 229 (1950).
149 *Foss, G. L.:* Lancet **6656**, 667 (1951).
150 *Bernard, J.:* Gynéc. et obstétr. **46**, 503 (1947).
151 *Ufer, J.:* Geburtsh. u. Frauenhk. **14**, 723 (1954).
152 *Burdine, W. E., et al.:* Fertility and steril. **8**, 255 (1957).
153 *Schockaert, J. A.:* Therapiewoche **12**, 270 (1962).

The embryonic and maternal factors which can lead to abortion are equally numerous[154].

*Maternal* causes include:

| |
|---|
| Organic genital tract disturbances (cervical insufficiency, abnormal positions of the uterus, hypoplasia* uterine malformations and pelvic tumours) |
| Poor nutrition of the zygote due to poorly developed endometrium* |
| General disturbances (infectious disease, blood incompatibilities, psychological trauma, cachexia) |

*Embryonic* causes include:

| |
|---|
| Lethal chromosome constitutions |
| Abnormal nidation |
| Placental insufficiency* |

* Endocrine causes.

The following *exogenous factors* should be mentioned:
Teratogens (thalidomide, cytotoxic drugs), drugs with a toxic effect, damage by irradiation, infection.

*Hormonal causes for Abortion:*

Death of the ovum in the first days or weeks of pregnancy, is usually due to damage occurring during implantation.
As shown on page 104, deficient decidual changes in the endometrium are also often found in patients who have early abortions. The zygote undoubtedly only thrives if it receives adequate supplies of glycogen and oxygen[155]. Abnormal nidation[156] with resultant placental abnormality[157] is said to be the sequel of inadequate endometrial development which is, in its turn, undoubtedly due to poor function of the ovaries in general and the corpora lutea in particular[157]. Constitutional, rather than hormonal deficiency cannot always be excluded in these cases. In cases of uterine hypoplasia, uterine growth may not keep pace with enlargement and development of the embryo. The sequel must be stretching and ischaemia of uterine muscle with the onset of uterine contractions.
Death of the embryo in the middle trimester is usually due to placental insufficiency which means deficient gaseous and metabolic exchange between mother and foetus and also inadequate formation of placental hormones. The time relationship between these developments is not known. Many investigators have shown that the excretion of pregnanediol and oestrogen falls some considerable time before the occurrence of abortion or premature labour.

*Endocrine investigation in cases of threatened abortion.* The clinical value of tests designed to detect impending intra-uterine embryonic death is disputed. Their widespread use is prevented by technical difficulties in their performance. In interpreting hormone excretion values, the day to day variations which occur in physiological conditions must not be overlooked. Twenty-four-hour urine assays must be repeated and this inconvenient and time-consuming sort of investigation should therefore be confined to selected cases. It is sometimes advisable to use a combination of several tests (e.g. pregnanediol estimations in conjunction with vaginal smears)[158].
Pregnanediol excretion and hence progesterone formation[159], may be temporarily or permanently reduced. It is said that abortion always occurs with values of under 5 mg. a day in the first trimester of pregnancy[160, 161]. If the pregnanediol excretion remains low in spite of adequate progestogen dosage, an unfavourable outcome is also likely[162].
The determination of oestrogens is of little value in the first trimester of pregnancy as the

[154] *Kaufmann, C., et al.:* Dtsch. med. Wschr. **84**, 347 (1959).
[155] *Hughes, E. C., et al.:* Amer. J. Obstetr. Gynec. **89**, 59 (1964).
[156] *Hertig, A. T.,:* Laboratory invest. **13** 1153 (1964).
[157] *Hughes, E. C., et al.:* Kongreßband Int. Gynäk. Kongreß Genf, Juli 1954, S. 715.
[158] *Timonen, S., & Göltner, E.:* Zbl. Gynäk. **81**, 1263 (1959).
[159] *Guterman, H. S.:* J. Amer. Med. Ass. **131**, 378 (1946).
[160] *Wenner, R., et al.:* Gynaecologia **143**, 159 (1957).
[161] *Borglin, N. E.:* Acta endocr. **22**, 49 (1956).
[162] *Borth, R., Gsell, M.*, a. *de Watteville, H.:* Acta endocr. **17**, 22 (1954).

levels normally seen are not yet very high (page 31).
The quantitative estimation of chorionic gonadotrophin has shown a considerable variation of values in normal pregnancy. With placental insufficiency, only a slow decrease in HCG excretion occurs (page 32). Quantitative HCG determinations are only of diagnostic value at the outset of pregnancy. For the diagnosis of ectopic pregnancy, see page 66.
Vaginal smears and the examination of cervical mucus are further diagnostic measures.

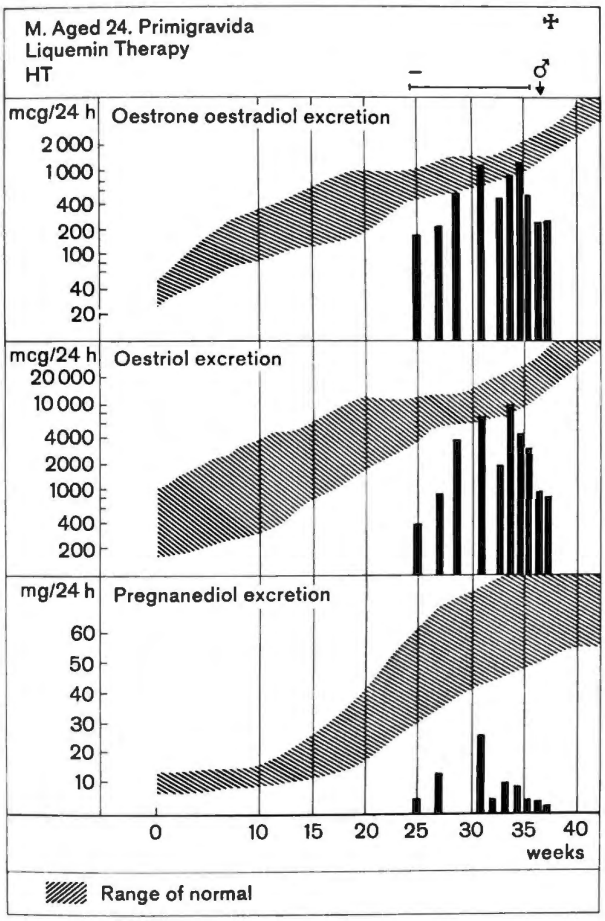



Figure 77. Hormone excretion pattern in a 24-year old primigravida with an intra-uterine death at 25 weeks. The foetus was retained until 37 weeks. (*Wenner, R., et al.:* Gynaecologia **143**, 182 [1957])

The vaginal smear develops a characteristic appearance in pregnancy as a result of the action of progesterone and oestrogens (page 31). The epithelial cells are large and have folded edges. Their nuclei are basophil and vacuolated. With impending embryonic or foetal death due to deficient progesterone secretion, the number of acidophil cells with pyknotic nuclei tends to exceed 30 per cent[163, 164, 169]. In other words, the picture of oestrogen effect appears. Due to the combined action of oestrogens and progesterone, the cervical mucus shows no "ferning pattern" (page 55). If the "ferning test" becomes positive and remains this way over longer periods, one must reckon that progesterone formation is diminishing and that death of the pregnancy from placental insufficiency is imminent[165–167].

*Possible types of hormone therapy and their value:* Hormones have only limited value in the treatment of threatened abortion[154] because:

- It is difficult to determine whether the embryo is alive or not at the start of treatment,
- Other, non endocrinological factors may operate,
- In cases where placental insufficiency means disordered hormone production, rational hormone therapy is hardly feasible as it has to be based on various complicated diagnostic procedures.

Hormone therapy is usually undertaken without good evidence of hormonal deficiency. Under these circumstances, the lack of success is hardly surprising. The expulsion of an embryo whose development has been disturbed can only be delayed and not prevented by hormone therapy. If bleeding in cases of threatened abortion is not controlled within 8 days, it is unlikely that pregnancy will progress[168].
Hormone therapy acts by improving the environment of an early pregnancy[169]. Decidual changes are promoted and uterine growth is enhanced. An added effect is relaxation of the uterus in the later months of pregnancy. Continuous progesterone alone can guarantee decreased responsiveness of uterine muscle to oxytocin before the onset of labour[170]. This

[163] *Abrams R. Y., & Abrams, Y.:* Fertil. & Steril. **15**, 84 (1964).
[164] *Mac Rae, D. Y.:* J. obstetr. gynaec. Brit. Commonw. **72**, 1038 (1965).
[165] *Zondek, B., et al.:* Fertility and steril. **6**, 523 (1955).
[166] *Macdonald, R. R.*, a. *Sharman, A.:* Internat. J. Fertil. **4**, 338 (1959).
[167] *Macdonald, R. R.:* J. Obstetr. Gynaec. **70**, 580 (1963).
[168] *Hörmann, G.:* Dtsch. med. Wschr. **74**, 274 (1949).
[169] *Swyer, G. s. M., & Little, V.:* J. obstetr. gynaec. Brit. Commonw. **72**, 1014 (1965).
[170] *Knaus, H.:* Zbl. Gynäk. **57**, 2658 (1933).

phenomenon is known as the "progesterone block"[171].

The statistical appraisal of the results of hormone therapy presents many problems. Cases in which abortion has been induced are difficult to exclude. If the products of conception are expelled within 48 hours after hormone treatment begins, it is likely that the pregnancy had already come to grief at an earlier date. This type of case will also influence statistics adversely. Adequate early treatment of threatened abortion, continued for sufficient lengths of time, will save the pregnancy in 70 to 80 per cent of cases[172–174]. Pregnant women who have more than three spontaneous miscarriages (habitual abortion) have poor prospects. None the less, the pregnancy can be saved in 40 to 70 per cent of cases[175, 176].

For hormone therapy in abortion prophylaxis, either oestrogens or progestogens can be used. The naturally occurring progesterone is hardly suited to this type of treatment as it is so rapidly metabolised that its parenteral administration leads to insufficient uterine concentrations of hormone[177]. By the use of more potent progestogens than progesterone, one increases the chances of setting the uterus at rest. It is also possible that this type of treatment prevents a progesterone deficit. Having regard to the high level of hormone production by the placenta, larger doses of hormone are required. It is said that oestrogens not only support uterine growth but also the formation of progesterone by the placenta[178, 179]. The latter hypothesis has not yet been confirmed. In pregnancy, oestrogens must also be given in relatively large doses.

A 10 to 1 combination of progestogen and oestrogen respectively, is undoubtedly the most physiological[180]. With hypoplasia of the genital tract, treatment with a combination of hormones is to be preferred. Treatment should be continued for several weeks after the time of risk. With a history of habitual abortion or previous premature labours, treatment should continue until the foetus is viable. Naturally, only those steroids should be used in pregnancy which are free of side effects on the foetus (page 26, 48).

**Treatment:**

1. Threatened abortion:
Progestogen therapy: Proluton Depot (Primolut Depot) 500 to 1000 mg. i.m. daily for four days, then 250 mg. daily. Further treatment as with cases of habitual abortion [181, 182]. Oestrogen therapy: Ethinyl oestradiol 0.2 to 0.6 mg. 3 to 6 times daily[183, 184].

2. Tendency to habitual abortion:
Proluton Depot (Primolut Depot) 250 to 500 mg. a week. Treatment should start as soon as possible after the first missed menstrual period[185].

3. Tendency to abortion in cases of uterine hypoplasia:
Proluton Depot (Primolut Depot) 250 to 500 mg. and Progynon Depot (Primogyn Depot) 10 mg. every week. Early institution of treatment essential.

4. Early abortion (see page 104).

5. Hormone therapy to prevent abortion after surgery (page 135)[186]:
Proluton Depot (Primolut Depot) 500 mg. preferably two to three days before operation. Further treatment with Proluton Depot (Primolut Depot) as in paragraph 1.

### b) Premature Labour

Hormone assays

A fall of oestrogens in urine and serum is a relevant diagnostic feature in the last tri-

171 *Bengtsson, L. Ph.;* Acta obst. gynec. Scand. **41**, 124 (1962).
172 *Castelazo Ayala, L.:* Ginec. obstetr. **8**, 167 (1953).
173 *Bishop, P. M. F.:* Brit. Med. J. **4671**, 130 (1950).
174 *Gitsch, E.;* Wien. klin. Wschr. **68**, 370 (1956).
175 *Davis, M. E., & Fugo, N. W.:* J. Amer. Med. Ass. **142**, 778 (1950).
176 *Davis, M. E. & Plotz, E. J.:* Recent Progr. Hormone Res. **13**, 347 (1957).
177 *Kumar, J., & Barnes, A.:* Bull. John Hopkins Hosp. **113**, 53 (1963).
178 *Smith, O. W., & Smith, V. G.:* Amer. J. Obstetr. Gynec. **58**, 994 (1949).
179 *Karnaky, K. J.:* Arizona Med. **8**, 36 (1951); Ref. J. Amer. Med. Ass. **145**, 1374 (1951).
180 *Vaux, N. W., & Rakoff, A. E.:* Amer. J. Obstetr. Gynec. **50**, 353 (1945).
181 *Neuweiler, W., & Berger, M.:* Fortschr. Geb. u. Gynék. **19**, 30 (1964).
182 *Rauscher, H.:* Symposium Uterusrelaxation, Bern 1963.
183 *Strahm, A.:* Geburtsh. u. Frauenhk. **13**, 823 (1953).
184 *Birnberg, Ch. H., et al.:* Amer. J. Obstetr. Gynec. **63**, 1151 (1952).
185 *Plotz, E. J.:* Med. Welt **1960**, 2134.
186 *Reifenstein, E. C.:* Ann. N. Y. Acad. Sc. **71**, 762 (1958).

mester[187–189]. With sudden falls in values, foetal death becomes a real possibility. The separate measurement of fractionated oestrogens has shown that oestriol excretion is affected first. Values under 1000 γ a day imply irreversible placental damage.

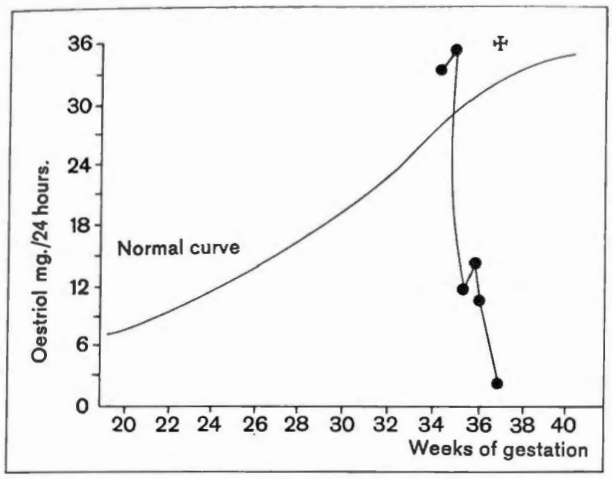



Figure 78. Rapid fall in oestrogen excretion just before intra-uterine death of the foetus.
(*Lauritzen, C.:* Deutsch. med. J. **14**, 644 [1963])

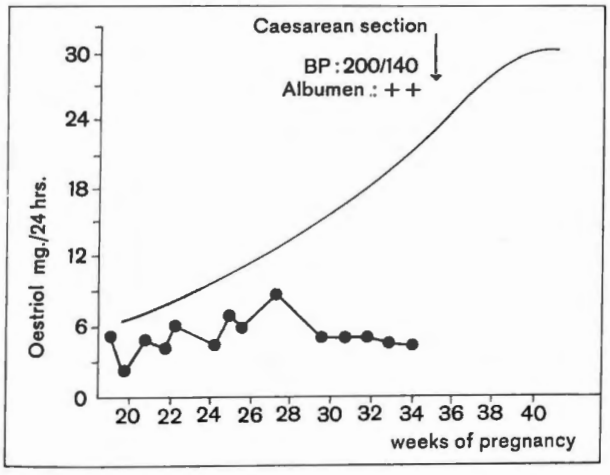



Figure 79. Oestrogen excretion with severe pre-eclampsia. The infant was saved by Caesarean section.
(*Lauritzen, C.:* Deutsch. med. J. **14**, 644 [1963])

**Treatment:**

Progestogens are the hormones mainly used for cases of threatened premature labour. Only very large doses can damp early uterine contractions. When the membranes have ruptured, it is only rarely possible to carry the pregnancy on to viability by using hormones[190].

Proluton Depot (Primolut Depot) 500 to 1000 mg. daily at first, then every 3 days. With ruptured membranes, Proluton Depot (Primolut Depot) 500 mg. daily.

### c) Hyperemesis Gravidarum

Pregnancy demands psychological and physical adjustment. The old-fashioned view about hyperemesis maintains that it is caused by metabolites from the developing foetus which have a toxic effect on the mother. Recent hormone research has shown that women with hyperemesis have a low urinary corticoid excretion[191]. A state of adrenal hypofunction, as with Addison's disease, thus exists. There are undoubted similarities between Addison's disease and hyperemesis gravidarum: in both conditions one sees peripheral circulatory failure, hypotension and electrolyte imbalance. None the less, it has not yet been proved that hyperemesis gravidarum is due to a failure of adrenal function[192]. It is more probable that the observed changes in adrenal function are the result of hyperemesis. This assumption gains support from the fact that injections of ACTH lead to an increase in corticosteroid excretion.

**Treatment:**

To date there has been little therapeutic application of the findings enumerated above. Sedatives, replacement of fluid and electrolyte losses, isolation of the patient and her psychotherapeutic support are the measures of primary importance. Other supportive measures are daily desoxy-corticosterone acetate[193] (Cortiron, Primocort) 5 to 10 mg., or Cortiron Depot (Primocort Depot) 50 mg. every 10 days.

### d) Pre-eclamptic Toxaemia

Water and salt retention, hypertension and, occasionally, albuminuria are features of this disorder. The risk of pre-eclampsia increases as pregnancy advances. The mother's life may be jeopardised by the onset of eclampsia.

[187] *Ittrich, G., & Igel, H.:* Zbl. Gynäk. **81**, 255 (1959).
[188] *Kubli, F., & Keller, M.:* Klin. Wschr. **41**, 861 (1963).
[189] *Frandsen, A., & Stakemann, G.:* Acta endocr. **43**, 184 (1963).
[190] *Eichner, E., et al.:* Amer. J. Obstetr. Gynec. **61**, 653 (1951).
[191] *Staemmler, H.-J.:* Arch. Gynäk. **182**, 561 (1953).
[192] *Elert, R.:* Arch. Gynäk. **183**, 48 (1953).
[193] *Staemmler, H.-J.:* Geburtsh. u. Frauenk. **18**, 1201 (1958).

The foetus is also endangered by the threat of placental circulatory disturbance[194].

Hormonal investigations in cases of pre-eclampsia have shown the following:

| |
|---|
| 1. The excretion of chorionic gonadotrophin is usually raised[195–196]. As a consequence, the ovaries of the neonate may show signs of overstimulation[200]. |
| 2. Oestrogen excretion is frequently diminished. A sharp fall in the oestriol fraction indicates poor prospects for the birth of a living child[201]. |
| 3. The excretion of adrenal corticoids is higher than normal at this time of pregnancy[202]. |
| 4. As compared to normal pregnancies, aldosterone excretion is diminished (page 32). Values resemble those usually found in the nonpregnant state[203]. |

These findings indicate that endocrine factors are of some importance in the aetiology of pre-eclampsia.

The points enumerated above may operate in the following way:

1. It is not certain by what mechanism raised chorionic gonadotrophin excretion comes about in the presence of a damaged placenta. In animal experiments, liver damage and changes in plasma proteins (both may occur in pre-eclamptics) have been produced by HCG[204]. It is thus possible that this hormone, whose function is ill-understood, can produce a sort of "pregnancy intoxication"—or pre-eclampsia.

2. See page 113.

3. The different corticoids are excreted in very varying amounts during different stages of pregnancy. Large amounts can be recovered from normal pregnancy urine after the 7th month. Still higher values occur with pre-eclampsia. These corticoid metabolites may come from the maternal or relatively large foetal adrenals if not from the placenta itself. It is certain, as evidenced by Cushing's syndrome, that excessive amounts of these hormones lead to salt and water retention, hypertension, and ultimately changes in plasma proteins[205]. An increase in the most important mineralocorticoid, aldosterone, has particularly adverse effects.

4. The fall in aldosterone excretion, taken in conjunction with a simultaneous rise of corticoid excretion, speaks for adrenal dysfunction. It must be remembered that the corticoids measured may not fully represent the amounts formed in the adrenals.

A number of interesting findings favour the hypothesis that pre-eclampsia is due to placental ischaemia. It is said that the disturbances in placental circulation which follow a placental infarct or an increase in uterine tone lead to production of a substance which causes hypertension, regardless of renal function at the time[206].

**Treatment:**

The originator of this theory[206] recommends that in cases where early delivery of the child is not a suitable line of management, treatment with uterine relaxants and progestogens is indicated (see treatment of abortion).

### e) Diabetes and Pre-eclampsia

Since the advent of insulin many more pregnant diabetics are seen in clinical practice. As a result of severe metabolic disturbances and pre-eclampsia, intra-uterine foetal death occurs. About 50 per cent of cases show some adverse changes in metabolism during pregnancy.

The risk to the mother is less than to the foetus[207]. According to White[208], the com-

194 *Berger, M., et al.:* Gynaecologia **154**, 14 (1962).
195 *Lloyd, Ch. W.:* Recent Progr. Hormone Res. **7**, 469 (1952).
196 *Loraine, J. A., & Matthew, G. D.:* J. Obstetr. **60**, 640 (1953).
200 *Philipp, E., & Stange, H. H.:* Dtsch. med. Wschr. **79**, 1519 (1954).
201 *Mastboom, J. L.:* Gynarcologia **134**, 217 (1952).
202 *Erb, H., et al.:* Zbl. Gynäk. **84**, 474 (1962).
203 *Stark, G.:* Arch. Gynäk. **192**, 519 (1960).
204 *Lax, H.:* Zschr. Geburtsh. **139**, 33 (1953); **145**, 113 (1956).
205 *Mastboom, J. L.:* Zbl. Gynäk. **75**, 801 (1953).
206 *Berger, M.:* Fortschr. Geb. u. Gynäk. **19**, 30, 118 (1964).
207 *Kade, H., & Dietel, H.:* Dtsch. med. Wschr. **77**, 673 (1952).
208 *White, P., et al.:* Amer. J. Obstetr. Gynec. **71**, 57 (1956).

plications seen in a diabetic pregnancy are due to hormonal imbalance, with increased chorionic gonadotrophin production[209] and diminished progesterone metabolism assured by the estimation of pregnanediol excretion. This imbalance has a particularly deleterious effect on the child in the last months of pregnancy. The baby may be large, its size and weight showing some correlation with maternal blood sugar levels[210]. The increased oxygen and metabolic demands made by too large a foetus cannot be met by a placenta whose function is already damaged by circulatory changes.

**Treatment:**

Adequate control of diabetes lessens the risk of developing pre-eclampsia. With a large baby, induction of labour or Caesarean section are commonly carried out at 36 to 37 weeks[211–213].

*Attention should be paid to the following details*[214]*:*

Prevention of acidosis by early correction of metabolic upsets.

Control or elimination of all infections.

Prevention of pre-eclampsia, hydramnios and renal insufficiency.

Delivery by the easiest route at an opportune time.

Meticulous care of the newborn.

The value of treatment with oestrogens[208], once favoured, is now doubted[215]. Insulin, diet and delivery at 36 to 37 weeks are said to be measures which, even without the addition of oestrogen therapy, offer the child good prospects.

N.B. Statistical analyses have shown[216] that a woman who delivers a large baby at term may develop diabetes at a future date. Glycosuria in the last trimester of pregnancy is particularly significant in such cases.

[209] *Loraine, J. A.:* Brit. Med. J. **4643**, 1946 (1949).
[210] *Pedersen, J.:* Acta endocr. **16**, 330 (1954).
[211] *Barns, H. H. F., & Morgans, M. E.:* Brit. Med. J. **4767**, 1058 (1952).
[212] *Bartelheimer, H.:* Ärztl. Wschr. **5**, 541 (1950).
[213] *Pease, J. C., et al.:* Brit. Med. J. **4718**, 1296 (1951).
[214] *Constam, G. R., et al.:* Schweiz. med. Wschr. **93**, 1647 (1963).
[215] *Council-Report:* Lancet **6895**, 833 (1955).
[216] *Beek, C. van:* 3. Symposion der Deutschen Gesellschaft für Endokrinologie, Springer-Verlag 1956, 124.

### f) Ectopic Pregnancy

At the beginning, the hormonal status is the same as with normal pregnancy. The corpus luteum of pregnancy forms progestogens and oestrogens while chorionic gonadotrophin is produced by the early, developing trophoblastic tissue. The patient has amenorrhoea and the endometrium shows decidual changes. Abnormal implantation soon leads to embryonic death. The output of chorionic gonadotrophin falls. The relatively insensitive "frog test" soon becomes negative[217]. Some HCG is still, however, produced by trophoblastic tissue. This can be detected by more sensitive tests (immunological pregnancy tests, vaginal smear tests, page 58) for some time after death of the embryo. As a result of a fall in chorionic gonadotrophin production, the corpus luteum produces diminished amounts of oestrogen and progestogen. This leads to endometrial bleeding, often the first symptom of ectopic pregnancy.

**Treatment:**

Hormonal treatment is pointless in cases of ectopic pregnancy.

### g) Hydatidiform Mole

If hydatidiform degeneration which usually occurs in the 3rd to 4th months of pregnancy affects a large part of the placenta, it leads to death and resorption of the foetus. The passage of vesicles, excessive uterine growth and high levels of gonadotrophin excretion (maintained after the fourth month of gestation) are diagnostic of this condition. The Langhans cells of the placenta are thought to be the site of chorionic gonadotrophin production. In cases of hydatidiform mole these cells are usually proliferated. Thus there may be histological evidence of raised HCG formation.

**Treatment:**

There is no hormone treatment.
Operative removal of the benign mole is necessary. Repeated quantitative estimations of HCG in urine should be part of the follow-up procedure in these cases, as residual vesicles may develop into chorion-epitheliomata.

### h) Chorion-epithelioma

While hydatidiform moles originate during pregnancy, chorion-epithelioma occurs after

[217] *Lewin, E.:* Geburtsh. u. Frauenhk. **13**, 832 (1953).

the birth of the foetus. This risk is particularly great in patients with hydatidiform moles.

The malignancy of chorion-epithelioma is very variable[218]. With chorion carcinoma or "chorion-epithelioma malignum", the names given to extremely invasive lesions, the haemorrhagic, partly infarcted tumour grows very rapidly, penetrating the uterine wall and forming lung metastases. A lethal outcome is invitable. In advanced cases, large amounts of HCG are formed and excreted. Values of 100,000 IU per litre of urine are not unusual. They are interpreted as indicating marked biological activity and malignancy.

In more benign cases, histologically indistinguishable from those just described[218], the tumour is only slightly invasive and the possibility of spontaneous regression or cure exists. A fall of HCG excretion is a favourable prognostic sign. The more benign forms of this disease are described as chorion-epitheliosis[219].

Repeated HCG estimations are of diagnostic and prognostic importance. Falling values offer favourable prospects while rising values indicate a gloomy outlook.

Occasionally, raised oestrogen and pregnanediol excretion has been observed in patients with chorion-epithelioma[220]. The diagnostic significance of these results is relatively slight.

**Treatment:**

The treatment of malignant chorion-epithelioma consists of radical surgery and radiotherapy.

Occasional successes with high dosage oestrogen or androgen therapy have been reported[221]. Hypophyseal inhibitors (weak oestrogens—paraoxypropiophenone) have also been used[222]. By inhibiting HCG formation by chorion-epitheliomatous tissue it was hoped to suppress the tumour's biological activity and to slow down its rate of growth. Except for isolated cases, probably classifiable as chorion-epitheliosis, no successes were reported. Treatment with anabolic steroids or androgens may, none the less, be palliative as in patients with other forms of genital tract carcinoma (page 129).

**i) Control of Uterine Contractions by Sex Hormones**

Oestrogens and progesterone promote uterine growth and relaxation of uterine musculature. Although the relaxant effect of progesterone was shown experimentally at an early stage[223], it was for a long time assumed that oestrogens could promote uterine contractions. It was even considered that oestrogens were abortifacient. This view was shown to be erroneous[224], although it still crops up from time to time[225]. *Hormones cannot be used to stimulate contractions in normal pregnancy.*

Hormone production only stops with interruption of the utero-placental circulation. It is therefore not a primary but a secondary event.

It has been assumed by many that oestrogen therapy can be used to induce labour at term or in cases of postmaturity[226, 227]. In practice, very variable and contradictory results have been obtained[228]. This type of steroid is also said to reduce the duration of labour. The large amounts of oestrogen produced in the last trimester of pregnancy and the function of hormones in pregnancy (page 34) do not suggest that oestrogens would be effective in inducing labour[231a]. The onset of labour appears to be the result of a very complex process the details of which are as yet unknown.

It has also been suggested that the progress of labour could be influenced by promoting softening of genital tract tissue and structures[229, 230]. Regular intra-muscular injections of progesterone or 17α-hydroxyprogesterone caproate (Proluton Depot or Primolut Depot 250 mg. every 14 days) together with vita-

[218] *Huber, H., & Hörmann, G.:* Geburtsh. u. Frauenhk. **12**, 511 (1952).

[219] *Novak, E. R., & Koff, A. K.:* Amer. J. Obstetr. Gynec. **20**, 153 (1930).

[220] *Kaufmann, C., & Zander, J.:* Acta endocr. **17**, 216 (1954).

[221] *Duffy, B. A.:* Amer. J. Obstetr. Gynec. **69**, 898 (1955).

[222] *Perrault, M., et al.:* Bull. mem. soc. med. hôp., Paris **1949**, 1008.

[223] *Knaus, H.:* Zbl. Gynäk. **57**, 2658 (1933).

[224] *Buschbeck, H.:* Münch. med. Wschr. **83**, 790 (1936).

[225] *Röseler, W. B.:* Heilkunst **64**, 367 (1951).

[226] *Kalkschmid, W., & Olbrich, E.:* Zbl. Gynäk. **75**, 1817 (1953).

[227] *Tapfer, S.:* Münch. med. Wschr. **102**, 621 (1960).

[228] *Klopper, A. J., & Dennis, K. J.:* Brit. Med. J. **5313**, 1157 (1962).

[229] *Contamin, R.:* Arch. Gynäk. **195**, 395 (1961).

[230] *Schulze, E. E.:* Zbl. Gynäk. **84**, 1942 (1962).

[231] *Ott, I., & Scott, J. C.:* Proc. soc. exp. Biol. Med. **8**, 48 (1911).

[231a] *Kaiser, R., & Will, J.:* Arch. Gynäk. **184**, 159 (1953).

min E have been used for this purpose during the last two trimesters of pregnancy. The resulting elasticity of soft tissue is said to be striking and it is claimed that labour is quick, painless and free of complications. There is, as yet, no proof to substantiate this suggestion.

### k) Control of Lactation

Lactation can be influenced by altering the endocrine status of the puerperium which is characterised by a lack of female sex hormones and prolactin secretion by the anterior pituitary (page 34).

It should be possible to improve lactation by using prolactin[232]. The results of trials with preparations containing this hormone are dubious. One can hardly expect to stimulate a gland in this way if it has been inadequately prepared by hormones during pregnancy.

Small doses of oestrogen cause transient increases in milk secretion in certain animals[233]. No satisfactory results have been obtained in humans. An increase in milk secretion may be produced by oxytocin (page 34) which increases the release of prolactin[231].

Optimal lactation is mainly achieved by an adequate fluid intake, prevention of breast engorgement, regular breast emptying and the neuro-humoral stimulus of the physiological sucking reflex.

Lactation can be suppressed by giving sex hormones in high doses. Oestrogens are most effective. Testosterone derivatives have a similar, if somewhat weaker effect[234]. Progesterone or various hormone combinations have also been used with success[235, 236]. The earlier this type of treatment starts, the more effective it is.

The intra-partum or post-partum use of sex hormones probably leads to inhibition of prolactin production by the anterior pituitary. In addition, oestrogens and progesterone, by direct action on breast epithelium, prevent its normal transition from proliferative to secretory function[237].

Treatment is more effective if it is started during labour rather than at a later stage.

**Suggestions for Treatment** (Suppression of Lactation):

1. Intra-muscular oestradiol benzoate or oestradiol valerate, 10 mg. on 2 to 4 consecutive days.
2. The injection of 2 ampoules of Duogynon (Primodos, Proluton Z fort).

The interruption of established lactation is more difficult. In women with a copious milk supply, a combination of several measures may be necessary. These include the use of a breast binder and fluid restriction. The dose of sex hormone used is the same or higher than the one employed for the suppression of lactation. It is occasionally difficult to arrest lactation which has been in progress for some time. If there is co-existent amenorrhoea, one must consider a possible organic disturbance of the anterior pituitary (page 85).

### l) Post-partum Endometritis

After abortion or normal delivery, endometritis may occur during a phase of deficient oestrogen excretion. This type of infection is not usually associated with much in the way of symptoms. Slight continuous blood loss, tenderness of the uterus and a slight fever are the characteristic signs. Oestrogens protect the uterus from a spread of infection by promoting uterine hyperaemia and endometrial regeneration[238].

Hormone therapy is effective in cases where infection is confined to the endometrium. Flagrant cases of puerperal sepsis with high temperatures should be treated with antibiotics.

**Suggestions for Treatment:**

Oestradiol benzoate 5 mg. on 2 to 3 consecutive days or oestradiol valerate (Progynon Depot or Primogyn Depot) × 1 to 2 within a week.

If treatment does not control bleeding or symptoms, a placental polyp or an adnexal infection may be preventing endometrial healing. In women who are breast feeding, milk production may be reduced as a result of treatment with oestrogens.

## VIII. Organic Disorders

### a) Fibroids

Fibroids develop and grow during the years of sexual maturity. After castration or following the menopause, fibroids stop growing

[232] *Editorial:* Brit. Med. J. 4772, 1340 (1952/I).
[233] *Hohlweg, W.:* Zbl. Gynäk. 69, 1299 (1947).
[234] *Dodek, S. M., Friedman, J. M., et al.:* J. Amer. Med. Ass. 154, 309 (1954).
[235] *Fiskio, P. W.:* J. Amer. Med. Ass. 158, 1322 (1955).
[236] *Kaiser, R., & Regensburger, E.:* Münch. med. Wschr. 94, 2029 (1952).
[237] *Fauvet, E.:* Arch. Gynäk. 178, 104 (1950).
[238] *Tietze, K.:* Zbl. Gynäk. 59, 1762 (1935).

or shrink[239]. In certain experimental animals, fibroids develop as a result of oestrogen administration[240]. These facts show that the growth of fibroids is supported by oestrogens. The reason for their development is, however, still unknown. Both androgens[241] and progestogens have a certain "anti-fibroid" effect. By inhibiting the anterior pituitary they diminish oestrogen production by the ovaries. It has not been shown whether these hormones also exert a direct effect on the fibroids. Testosterone is said to diminish the uterine circulation[242].

There is no uniformity of opinion about surgical versus hormonal treatment (including castration)[243]. It must be accepted that progestogens and androgens can reduce the size of fibroids[245] and also that when these hormones are withdrawn, the fibroids grow again in response to re-established ovarian function.

Hormone therapy does not, however, seem indicated in sexually mature women, the interval before the menopause being too great. Surgical treatment is preferable and myomectomy is superior to hormone therapy in women who still desire children.

| In the following circumstances hormone therapy is not indicated[244, 245]: |
|---|
| Very large tumours, |
| Evidence of rapid growth (suspicion of sarcoma), |
| Uncertain diagnosis, |
| Pain, |
| Presence of anaemia due to blood loss (provided it is not so severe as to preclude surgery), |
| Pregnancy, |
| Co-existent carcinoma of the endometrium or cervix, |
| A desire for more children. |

These limitation make only the following groups suitable for hormone treatment:

Older patients in whom a menopause is imminent.

Patients who are unfit for operation because of obesity, hypertension, heart disease etc.

Patients who are unfit for operation because of severe anaemia due to menorrhagia. Hormone therapy may be a useful stop-gap while these patients are made fit for operation.

If side effects are to be avoided progestogen therapy is best as treatment usually has to continue for some time.

**Suggestions for Treatment:**

1. Tablets of Primolut N, 2 to 3 daily from the 16th to 26th day of the cycle[246].

2. Continuous treatment with Primolut N, 2 tablets daily, as for cases of endometriosis.

3. Delay of menstruation (to suit preparations for operation or to help with treatment of anaemia)

a) for delay of a few days:

One ampoule of Primosiston some 3 days before the expected onset of menstruation.

b) for a delay of one to two weeks:

Three tablets of Primolut N and 2 tablets of Progynon C (Primogyn C) daily for a period of one to two weeks starting on the 26th day of the cycle.

### b) Endometriosis

Foci of endometriosis show proliferative activity (as does normal endometrium) in response to the cyclical production of hormones by the ovary. Premenstrual pain and congestion are the inevitable sequel of the gradually cumulative effect of hormones which characterise this phase of the cycle. Reddish-blue discoloration of visible foci in the vagina or cervix may be easily detected. With the onset of menstruation, the endometrial foci diminish in size. During this phase no oestrogens are being produced by the ovaries.

Until recently, testosterone was used in the treatment of endometriosis because the vasoconstrictive and anti-gonadotrophic actions of this drug caused some improvement in symptoms[247]. It has been replaced by pro-

[239] *Seitz, L.:* Münch. med. Wschr. **24**, 1281 (1911).
[240] *Lipschutz, A.:* Steroid Hormones and Tumors, Baltimore 1950.
[241] *Reifferscheid, W.:* Zbl. Gynäk. **65**, 420 (1941).
[242] *Abarbanel, A. R.:* Amer. J. Obstetr. **38**, 1043 (1939).
[243] *Wenner, R.:* Grundriß der gynäkologischen Endokrinologie, Basel 1952.
[244] *Newman, H. T.:* Amer. J. Obstetr. Gynec. **68**, 1489 (1954).
[245] *Bleier, W.:* Geburtsh. u. Frauenhk. **17**, 463 (1957).
[246] *Kaiser, R.*, u. *Fink, P.:* Med. Klin. **56**, 429 (1961).
[247] *Hoffmann, Fr.:* Geburtsh. u. Frauenhk. **8**, 806 (1948).

gestogens which rapidly alleviate symptoms and may lead to complete regression of this somewhat obstinate disease process[248–252]. Histological studies have shown decidual reaction and oedema in the endometriotic areas. At a later stage, endometrial tissue disappears completely and is replaced by fibrosis.

**Treatment:**

Cyclical or continuous therapy may be used. Both suppress ovulation. Treatment should continue for at least 6 months. Small foci of endometriosis will disappear much earlier. After treatment is discontinued, biphasic cycles are again established.

**Suggestions for Treatment:**

1. Continuous therapy[248, 250, 251] with 2 tablets of Primolut N daily. If bleeding occurs, the dose should be increased to three tablets daily.

2. Cyclical therapy[249, 252]: One tablet of Anovlar 21 or Gynovlar 21 from the 5th to 25th days of the cycle.

### c) Mastodynia

Mastodynia is cyclical swelling and tenderness of the breasts without any associated organic or pathological changes. It occurs at the time of most intense hormonal activity—the premenstrual phase—and is often associated with other manifestations (page 96). Premenstrual treatment with oestrogens tends to aggravate breast symptoms[253]. There is thus an undoubted connection between ovarian function and these ill-understood, cyclical, congestive changes in the breast which may give troublesome symptoms for a period of years. The cause, not yet proven, is usually said to be a relative premenstrual excess of oestrogens[255], due either to their increased formation[254] or their decreased breakdown[256].

[248] *Kistner, R. W.:* Amer. J. Obstetr. Gynec. **75**, 264 (1958).
[249] *Peeters, F., et al.:* Scalpel **114**, 1111 (1961).
[250] *Helpap, B.:* Geburtsh. u. Frauenhk. **23**, 539 (1963).
[251] *Lax, H.:* Zbl. Gynäk. **83**, 524 (1961).
[252] *Chalmers, J. A.:* J. Obstetr. Gynaec. Brit. Empire **69**, 801 (1962).
[253] *Ufer, J.:* Geburtsh. u. Frauenhk. **14**, 723 (1954).
[254] *Béclère, Cl.:* Gynéc. prat. **3/4**, 268 (1952).
[255] *Pundel, J. P.:* Gynéc. prat. **3/4**, 237 (1952).
[256] *Smith, O. W., & Smith, V. G.:* Amer. J. Obstetr. Gynec. **39**, 405 (1940).

Some maintain that women with mastodynia show a somewhat higher incidence of breast carcinoma but that has certainly not been established or proved[257].
See page 47 for an account of the connection between oestrogens and tumour growth.

**Suggestions for Treatment:**

Two tablets of Primolut N daily from the 18th to 26th days of the cycle[258].

### d) Fibro-adenosis (chronic interstitial mastopathia)

In fibro-adenosis of the breast there are sometimes painful nodular changes in breast tissue due to a benign process in which proliferative epithelial changes occur together with the formation of small cysts[259]. Watery or blood-stained secretion may be obtained from the breast from time to time. The hormonal factors relevant to mastodynia are among those which operate in this condition. Symptoms tend to be maximal in the premenstrual phase and decrease with the decline in ovarian function which follows.
Breast carcinoma is an all important differential diagnosis so that excision biopsies and histological examination of any circumscribed lesion should always be made. Where the breasts show diffuse nodularity and the nodules are small (shotty breast), symptoms may be particularly troublesome and may be treated with androgens. Testosterone apparently has a direct anti-proliferative anti-oestrogenic action on breast tissue. Direct intra-mammary injections into affected sites are often more effective than intra-muscular therapy[260].

**Treatment:**

1. Local fibro-adenosis: Intra-mammary Testoviron (Primoteston) 25 mg. every two to three days at first and later at longer intervals. A total of about 5 to 10 injections should be given.

2. Diffuse fibro-adenosis: The treatment is the same as for mastodynia.

[257] *Gummel, H.:* Dtsch. Gesd.wes. **8**, 797 (1953).
[258] *Cuningham, K., & Lang, W. R.:* Med. J. Austral. **49**, 341 (1962).
[259] *Konjetzny, G. E.:* Pathologie, Klinik und Behandlung der Mastopathie, Stuttgart (1942).
[260] *Elert, R.:* Gynéc. prat. **3**, 139 (1952).

### e) Mammary Hypoplasia and Hyperplasia

The female breast may be as underdeveloped in otherwise normal women as it is in patients with infantilism. A limited increase in the volume of breast tissue may occur with oestrogen treatment. But it must be remembered that breast tissue consists not only of glandular elements but also of fat which cannot be influenced by hormones[261].
In patients who are thin, weight increase may therefore be desirable.

**Suggestions for Treatment:**

1. In sexually mature women, anointment of breast skin with oestrogen creams may be useful[262, 263]. Skin areas bearing moles or pigmented warts should be avoided.

2. With deficient genital tract development, breast growth may be enhanced by a state of "pseudo-pregnancy" (page 97).

Abnormally large breasts are usually due to an increase of fatty tissue. Only operative measures can reduce their size.

### f) Pelvic Inflammatory Disease

Severe adnexal inflammations cause exudates, cellular proliferation and infiltration in affected sites and in neighbouring areas. After the disease has subsided, residual parametrial and adnexal induration may be found. The known anti-inflammatory effect of glucocorticoids on mesenchymal tissue led to their use in the treatment of adnexal infections[264–266].
In subacute cases or acute cases with fever, simultaneous treatment with antibiotics is essential. The body's local response to inflammation is suppressed by prednisolone. Without antibiotics, therefore, the causative organism would spread without restriction. With treatment, fever rapidly subsides as inflammatory changes regress. Parametrial or adnexal swellings disappear. Considerable cellular infiltrates and induration can disappear relatively rapidly. Sometimes it is even possible to prevent tubal occlusion and to preserve tubal function.

**Treatment:**

1. In acute and subacute cases:

*Day 1:* Preliminary treatment with a broad-spectrum antibiotic.

*From Day 2:* Prednisolone tablets, 50 to 70 mg. daily with antibiotics.

Combined therapy for 10 to 14 days with gradual reduction of prednisolone dosage by 5 mg. a day.
Three consecutive injections of ACTH 20 IU after discontinuing prednisolone. Treatment with antibiotics should continue during this time.

2. In chronic cases[267]:

Prednisolone tablets, 10 to 15 mg. daily until there is clinical response. In cases where there is exacerbation, further treatment is as for acute cases.

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[261] *Burger, K.:* Med. Klin. **45**, 286 (1950).
[262] *Bickenbach, W.:* Dtsch. med. Wschr. **76**, 1032 (1951).
[263] *Kneer, M.:* Dtsch. med. Wschr. **72**, 681 (1947).
[264] *Anselmino, K. J.:* Geburtsh. u. Frauenhk. **18**, 215 (1958).
[265] *Hüter, K. A., & Hartmann, P.:* Geburtsh. u. Frauenhk. **18**, 1223 (1958).
[266] *Günther, H. E.:* Med. Klin. **53**, 1270 (1958).
[267] *Staemmler, H.-J.:* Geburtsh. u. Frauenhk. **18**, 1201 (1958).

# L. Treatment of Climacteric Disturbances and the Sequelae of Castration

Climacteric symptoms are by no means an invariable occurrence. Menstrual bleeding remains regular until the menopause which is due to cessation of ovulation and diminished oestrogen secretion by the ovarian follicles. A healthy, adaptable individual rapidly settles down to her new status with a minimum of troublesome symptoms.

More commonly, however, patients experience symptoms before or after the menopause and these often require a period of treatment. These symptoms are due to a gradual loss of ovarian function (figure 14).

One can distinguish between those symptoms which are the acute result of ovarian insufficiency and those disorders which assume importance many years after the menopause. The average life expectancy of a woman in our generation is 60 to 70 years. Thanks to advances in medicine and general hygiene, this constitutes a favourable contrast to earlier centuries. Ovarian function has not, of course, kept pace with the increase in life expectancy. It fails in the fourth decade of life[1]. Thus women are deprived of ovarian function for a relatively large part of their lives. This results in an often tragic situation to which insufficient significance and respect have, to date, been attached. This physiological disturbance leads to numerous mental and physical complications which doctors often tend to neglect[2].

## I. Disturbances before the Menopause

Disturbances of rhythm such as oligomenorrhoea (page 92), polymenorrhoea (page 93) and hypermenorrhoea (page 95) are relatively common. They are mainly caused by a failure of ovulation (the recession of reproductive function). Treatment is only necessary when heavy blood loss occurs. For suggestions concerning treatment, the sections relative to each symptom should be consulted. Dysfunctional bleeding due to cystic glandular hyperplasia (page 90) is a more serious disturbance. Unless there is a contra-indication, diagnostic curettage should be made in order to exclude organic disease of the uterus. The second measure is to prevent recurrent abnormal bleeding by treatment with cyclical pro-

[1] *Wenner, R., & Hauser, G.:* Ergebn. inn. Med. 16, 125 (1961).

[2] *Wilson, R. A., & Wilson, Th. A.:* J. Amer. Geriatr. Soc. 11, 347 (1963).

gestogens (page 90). As the disorder can only be of limited duration, surgical or radiotherapeutic treatment of cystic glandular hyperplasia need only be considered in very selected cases.

## II. Disturbances after the Menopause

(The hypergonadotrophic phase, page 35)

Symptoms most commonly appear after the menopause. At the beginning, they are due to mental disturbances or changes in autonomic function. Women who have experienced the latter previously are particularly prone to develop hot flushes, sweats, tachycardia and circulatory disturbances[3]. Not all these cases require treatment. It must be remembered however that career women may suffer considerably with menopausal symptoms. In them, therapy is often indicated in order to keep them happy at work[4]. The type and duration of treatment must depend on the details of any individual case[5]. Where symptoms are slight, reassurance and adjustment of the pattern of living by prescribing hydrotherapy (e.g. sauna baths) may be very effective.

An effort, often rather futile, should be made to control obesity by diet. Sedatives should be prescribed for states of irritability. Sedation by day may be refused by patients who go to work. With symptoms of moderate or greater severity, hormone therapy is preferable to all other forms of treatment. A mixture of androgens and oestrogens is effective in controlling symptoms and, even with prolonged use, leads to no undesirable side effects[6] (page 22). Menopausal symptoms usually disappear rapidly. Insomnia, hot sweats, and hot flushes give way to a general feeling of well-being[7]. Patients often comment spontaneously about favourable increases in mental activity and a welcome return of mental balance.

In many cases, the ideal described is not achieved for the following reasons:

1. After the menopause the endometrium may be in a state of high proliferative activity[8]. Patients of this type easily develop vaginal bleeding in response to any form of hormone therapy[4]. These bleedings, although harmless, cause doctor and patient sufficient anxiety to warrant diagnostic curettage.

2. In subjects who are particularly sensitive to the effect of androgens, a mixture of oestrogens and androgens may lead to virilization even though only standard doses are employed. Hoarseness (usually reversible) and lowering of the voice (usually irreversible) are extremely unpleasant[9].

The duration of treatment varies from a few weeks to several years. The longer treatment is carried out, the greater the danger of virilization.

It is advisable to give repeated but limited courses of treatment. In the intervals without therapy, it can be determined whether symptoms persist. It should be realized that hormones are drugs and should not be used as tonics. There is almost no absolute contraindication to treatment with an oestrogen-androgen mixture. It can even be applied to women who have had a breast or genital tract cancer or who have fibroids as this drug combination has no oestrogenic effect[10, 11].

**Suggestions for Treatment:**

Treatment with oestrogens:

1. One injection of a depot oestrogen, Progynon Depot (Primogyn Depot) 10 mg. every 3 to 4 weeks.

2. One tablet of Progynon C (Primogyn C) daily.

Therapy using a hormone mixture:

1. One injection of Primodian Depot.
After an interval of 3 weeks, one tablet of Primodian daily.
Subsequently, an interval without treatment.

2. With severe cases:

One ampoule of Primodian Depot every 3 to 5 weeks.

## III. Castration

Castration leads to a severe and sudden change of hormone balance. The symptoms caused by removal of the gonads and hyperfunction

[3] *Molitor, K.:* Deutsch. Gesd.wes. 9, 1411 (1954).
[4] *Ufer, J.:* Med. Klin. 51, 471 (1956).
[5] *Martius, H.:* Dtsch. med. Wschr. 79, 304 (1954).
[6] *Glass, S. J.:* J. Clin. Endocr. 10, 1616 (1950).
[7] *Schneider, J. A.:* Medizinische 1953, 923.
[8] *Lajos, L., et al.:* Zeitschr. Geburtsh. u. Gynäk. 159, 308 (1963).
[9] *Arndt, H. J.:* Deutsch. med. Wschr. 88, 2336 (1963).
[10] *Geese, K., & Wied, G. L.:* Ärztl. Wschr. 8, 712 (1953).
[11] *Pots, P.:* Ärztl. Wschr. 8, 1194 (1953).

of the anterior pituitary are often much more marked than those of menopausal origin[13]. As with climacteric women, treatment with a mixture of hormones is probably best.

It has been shown that premature loss of ovarian function carries a risk of subsequent illness, particularly osteoporosis. Thus substitution therapy with sex hormones should even be given to women who are relatively symptom free. In some cases, treatment with a mixture of hormones can be replaced by cyclical therapy with oestrogens and progestogens as in cases of amenorrhoea (page 81). This leads to menstrual-type bleeding and provides a woman with a psychological boost.

## Suggestions for Treatment:

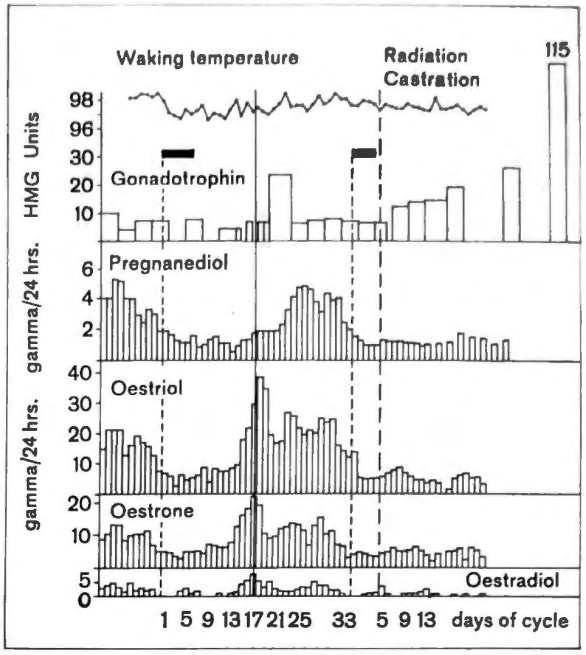


Figure 80. The effect of X-ray castration on the gonadotrophin, pregnanediol and oestrogen excretion.
(*Brown, J. B. & Matthew, G. D.:* Recent Progr. Hormone Res. **18**, 337 [1962])

[13] *Nathanson, I. T., et al.:* Amer. J. Obstetr. Gynec. 40, 936 (1940).

# M. Treatment of Disturbances Arising After the Climacterium

Post-climacteric disturbances are due to failure of ovarian function and, in contrast to symptoms of the climacterium, are organic in origin. The most widely publicized of these, osteoporosis and arterial disease, are not discussed here as they are outside the realm of gynaecology.

There is a time-relationship between the loss of ovarian function and the appearance of trophic disturbances. Women who have had an early menopause or whose ovaries were removed tend to develop these disturbances relatively early[1].

## I. Vaginal Changes in Elderly Women

The vagina of elderly women is less vascular, thin and contains only scanty secretions. Marked atrophy may occur in nulliparous patients. Atrophic changes may be confined to the posterior fornix or may affect the whole vagina.

The local use of oestrogens in the form of cream or pessaries leads to increased vascularity and improvement in the size and elasticity of the vagina. Their use may prevent constrictive dyspareunia.

The relative deficiency of glycogen in postmenopausal vaginal epithelium makes it particularly susceptible to infection and inflammation. A specific type of senile vaginitis, colpitis vetularum, should be mentioned.

Senile vaginitis, like vaginitis in childhood, responds much more readily to treatment with oestrogens than vaginal infection occurring during the reproductive era[2]. Local oestrogens have a much more marked effect than parenteral or oral therapy which has the added disadvantage of provoking endometrial bleeding all too easily. Treatment with oestrogens, if it has to be given, should be of short duration.

Benign vaginal ulceration due to pessaries or concretions responds well to local treatment with oestrogens. In elderly patients any vaginal wound heals more quickly with direct applications of oestrogens[3].

**Suggestions for Treatment:**

1. Oestrogen creams (intra-vaginal cream twice a week) are preferable to pessaries in this type of disorder.

---

[1] *Nowakowski, H.:* Internist 3, 219 (1962).

[2] *Sjöstedt, S.:* Acta endocr. 12, 260 (1953).

[3] *Falk, H. C., & Hanid, R.:* J. Amer. Geriatr. Soc. 11, 1152 (1963).

2. To begin with, suppurative vaginitis should be treated by a combination of antibiotics and oestrogens. Further treatment as under paragraph 1.

3. Vaginal cream combined with oestradiol benzoate 5 mg. intramuscularly 2 injections with 3 days' interval.

## II. Pruritus and Kraurosis Vulvae

According to their aetiology, the following types of pruritus can be distinguished[4, 5]:

As a result of psychoneurosis, nerve endings are over-sensitive.

Pruritus due to deficient personal hygiene, particularly in places of work which are excessively dusty.

Pruritus of endocrine origin.

Pruritus with diabetes.

Pruritus provoked by oxyuris infections or vaginal discharge.

Oestrogen creams can be tried in women after the menopause[6] provided the presence of other endocrine causes can be excluded. Systemic, high dose oestrogen therapy is out of the question in these cases[7].
In the presence of vulval skin changes, hydrocortisone cream is indicated provided aetiological factors such as vaginal discharge and general metabolic disturbance have been excluded or treated. Early cases of kraurosis vulvae (a condition which has an association with rhagades) where the labia minora are most markedly affected by atrophic changes, may be treated by local applications of oestrogen cream. In advanced cases, vulvectomy is indicated.

**Suggestions for Treatment:**

1. Local application of oestrogen cream immediately after vulval toilet.

2. Topical corticoids (Scheroson F or Ultralanum) for cases of pruritus with eczema.

## III. Pyometra

Pyometra may follow cervical stenosis in elderly women. Apart from mechanical treatment (i.e. dilatation of the cervical canal) antibiotics and oestrogens may be indicated[8]. First, however, endometrial carcinoma must be excluded.

**Additional Therapy:**

Oestradiol benzoate 5 mg. intramuscularly 3 injections at intervals of 3 to 4 days.

## IV. Climacteric Trigonitis

During the climacteric, the irritable, hypersensitive bladder may cause a symptom complex which is distinct from the trouble caused by acute and chronic cystitis[9]. Frequency and urgency, which are particularly marked in cold weather are the main symptoms. Apart from reddening of the trigonal area of the bladder, there are no abnormal findings. Oestrogenic and androgenic hormones regulate the bladder musculature and sphincter mechanisms.

**Treatment:**

Primodian Depot every 3 to 4 weeks in combination with warmth and spasmolytic drugs.

## V. Stress Incontinence

Stress incontinence in women is usually due to an anatomical disturbance of the bladder sphincter caused by trauma. Operative treatment of associated anterior vaginal wall prolapse is indicated.
Quite frequently, incontinence may occur during or after the climacteric in cases where there is no history of trauma to sphincter mechanisms. In these cases, there is probably disorder of the bladder sphincter, its function largely depending on the presence of sex hormones. Provided that they are used in combination with conservative measures (pelvic floor exercises, faradism) treatment with a combination of oestrogens and androgens has been proved to be of particular value[10].

**Suggestions for Treatment:**

Primodian Depot (one injection every 2 weeks) or one tablet of Primodian 3 times a day.

[4] *Tscherne, E.:* Med. Klin. 47, 1598 (1952).
[5] *Ackermann, Fr.:* Ärztl. Praxis 4, 1 (1952).
[6] *Klaften, R.:* Med. Klin. 33, 566 (1937).
[7] *Buschbeck, H.:* Zschr. Geburtsh. 110, 1 (1934).
[8] *Tscherne, E.:* Sexualhormontherapie, Wien, S. 42 (1949).
[9] *Hesse, F.:* Medizinische 1955, 686.
[10] *Gitsch, E., & Brandstetter, F.:* Zbl. Gynäk. 78, 820 (1956).

# N. Hormone Therapy for Carcinoma

## I. Mammary Carcinoma

### a) Introductory Remarks

Breast carcinoma occupies a special position among the malignant tumours in women because it is, to a certain degree, hormone dependent. Its growth can be suppressed or stimulated by hormones. Endocrine therapy cannot, however, lead to complete disappearance of a carcinomatous lesion. Surgery and radiotherapy should, therefore, be the first measures wherever possible. Endocrine measures should only be considered in cases where no response to operation or radiotherapy can be expected.

*The effect of hormones on tumour tissue*

In cases which respond to treatment, attempts have been made to study the effect of hormone therapy by repeated tumour biopsy and measurement of calcium excretion. It has been shown that connective tissue formation is enhanced in soft tumours[1]. Several months after starting hormone treatment, the cancer cells become enclosed in a network of thick fibrous tissue strands which constitute a barrier to tumour spread. In addition, hormone therapy can diminish the decalcification which occurs around bony metastatic lesions. Signs of bone destruction may disappear. Sometimes an unfavourable reaction, in the form of increased calcium excretion, may be observed with hormone therapy[2].

*Sex chromatin and mammary carcinoma*

Only a proportion of patients with breast carcinoma respond to treatment which is aimed at causing alterations in the endocrine system. In making attempts to distinguish between hormone dependent and hormone resistant tumours, histological appearances are not helpful[2b].

Some authors state that the different reactions of breast carcinoma to hormone therapy reflect sex differences between tumours[3, 4].

It is claimed that a distinction can be made between male and female tumours by a quantitative study of the Barr bodies in

[1] *Emerson, W. J., & Kennedy, B. J.:* Cancer 6, 641 (1953).

[2] *Kennedy, B. J., et al.:* Cancer Res. 13, 445 (1953).

[2b] *Huggins, C., & Scott, W.:* Am. Surg. 122, 1031 (1945).

[3] *Blümel, C., et al.:* Wien. Klin. Wschr. 75, 41 (1963).

[4] *Kimel, V. M.:* Cancer 10, 922 (1957).

tumour cell nuclei (page 60). Fifty per cent of breast carcinomas are said to be "male" and responsive to "female hormones" (oestrogens). This assumption is not generally accepted[5]. It is quite possible that the second X chromosome which is said to be rather labile is lost in tumour cells[5] and that their male sex is therefore only due to this phenomenon.

*Different types of hormone therapy and their value*[6]

One can distinguish between treatment which deprives the body of hormones and measures which increase hormone levels. Castration, adrenalectomy and hypophysectomy which are forms of ablative endocrine surgery constitute the first group. The second type of treatment, which Huggins[6b] describes as being based on the "interference effect", includes therapy with oestrogens, progestogens and corticoids. The results of these different forms of therapy are strikingly similar.

### b) Castration

This method of treatment, first used by Schinzinger[7] and Beatson[8], leads to transient remissions in 40 per cent of sexually mature women. It is said that after a time, the adrenals cancel out the beneficial effect of hormones by secreting increased amounts of oestrogens (figure 81). If castration does not inhibit tumour growth, it can be assumed that the neoplasm is not oestrogen dependent. Radiotherapeutic ablation of ovarian function cannot replace oophorectomy as ovarian metastatic deposits of breast carcinoma are best dealt with surgically. Castration appears to diminish the risk of recurrence. It can also be used as a prophylactic measure following removal of the primary carcinoma[9].

### c) Adrenalectomy

Adrenalectomy is recommended for cases of breast carcinoma if improvement after castration is not maintained[10]. It is probable that the beneficial effect of adrenalectomy (objective improvement in 45 per cent of cases for an average of 9 months) is due to removal of the remaining source of oestrogens. In cases of breast carcinoma, the hormone produced by this source may be considerable. Simultaneous adrenalectomy and bilateral oophorectomy does not increase the duration of a remission. Treatment with cortisone is necessary after adrenalectomy. Surgical removal of the adrenals cannot be replaced by irradiation of these glands.

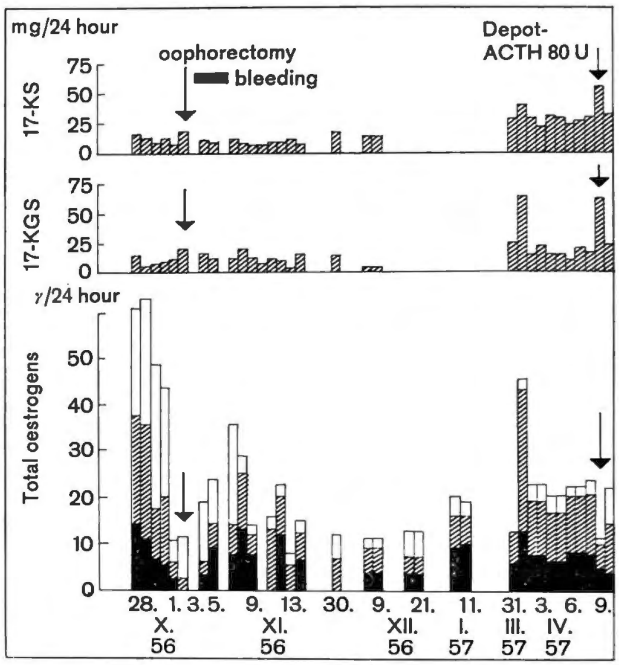


Figure 81. Excretion patterns of 17-ketosteroids (17-KS), 17-ketogenic steroids (17-KGS), oestrogens (□ oestriol, ▨ oestrone, ■ oestradiol 17-β) in a 46-year old patient with breast carcinoma, before and after oophorectomy and under the effect of ACTH stimulation.
*Bayer, J. M., Breuer, H. & Nocke, W.*, (Langenbecks Arch. klin. Chir. **288**, 84 [1958])

### d) Hypophysectomy

Complete removal of the pituitary leads to atrophy of the ovaries and adrenals. The advocates of this method attach particular value to the loss of growth hormone and prolactin which follows surgery. English and American authors have used this treatment extensively as it does not carry a significant increase in operative risk[11, 11a]. In all age

[5] *Zanella, E., et al.:* Zschr. Krebsforsch. **64**, 83 (1961).
[5] *Pearson, O. H., et al.:* J. Amer. Med. Ass. **159**, 1701 (1955).
[6b] *Huggins, C., et al.:* Proc. Math. Acad. Science U.S. **48**, 379 (1962).
[7] *Schinzinger, L.:* Münch. med. Wschr. **52**, 1724 (1905).
[8] *Beatson, G. T.:* Lancet **2**, 104 u. 162 (1896).
[9] *Schmidt-Überreiter, E.:* Wien. klin. Wschr. **69**, 289 (1957).
[10] *Huggins, C., & Dao, T. L. Y.:* J. Amer. Med. Ass. **151**, 1388 (1953).
[11] *McCalister, A., et al.:* Brit. Med. J. **5226**, 613 (1961).
[11a] *Atkins, H. Y. B., et al.:* Lancet 7135, 1148 (1960).

groups, a remission rate of 50 per cent can be expected. Its duration is 1 to 2 years or even longer[12]. Treatment with cortisone is indicated after hypophysectomy. Irradiation of the pituitary cannot replace hypophysectomy. Radium-gold implantation equally does not lead to a complete loss of pituitary function.

### e) Treatment with Anabolic Steroids or Testosterone Esters

It is treatment with androgens, originally due to *Loeser*[13], which is most frequently employed. It leads to a change in hormone environment, an inhibition of gonadotrophin production and anabolic changes. The drug also causes euphoria. Treatment with androgens is successful before and after the menopause. The resulting calcification in bony metastases is particularly impressive. Just occasionally, androgens may cause rapid growth of bony secondaries.

Calcium measurements in blood and urine are therefore necessary if the patient's condition deteriorates. The results are only slightly inferior to ablation therapy. There is subjective improvement in 80 per cent of cases treated. Objective evidence of remission can, however, be shown in only 25 per cent of cases treated[14]. The treatment of advanced cases which have no prospect of cure should continue as long as possible, as rapid progress of the disease may be the consequence of stopping treatment. Virilization and an increase in libido are side effects which have to be accepted. The use of weak androgenic substances meets with no success[15, 16].

Testosterone therapy is not only recommended for advanced cases but also as a prophylactic measure aimed at preventing recurrences[17].

Treatment with anabolic steroids seems to have equally good results[18, 19].

### f) Treatment with Oestrogens

This type of therapy is only indicated after the menopause and from about 55 years of age onwards. It has been shown that treatment with oestrogens is preferable to androgen therapy in older women. Virtually nothing is known about the method of action. Objective improvement is achieved in 44 per cent of cases for an average of 8 months. Lesions in soft tissues, (e.g. the primary tumour, local recurrences, lung metastases[20]) are particularly responsive while peritoneal metastases seem to resist treatment[21]. It is always possible that treatment will lead to exacerbations of lesions which are situated in soft tissues or which are osteolytic. Determinations of calcium in urine and blood are therefore necessary. Uterine bleeding is no indication for discontinuing therapy. It usually stops spontaneously.

### g) Treatment with Cortisone

The continuous administration of cortisone or cortisone derivatives inhibits anterior pituitary ACTH production and leads to adrenal atrophy. A relative deficiency of adrenal steroids occurs (glucocorticoids, androgens, oestrogens). The results published to date show that transient objective improvement occurs in 40 per cent of cases[22]. This type of treatment is indicated as soon as a patient comes out of a remission following castration.

### h) Progestogen Therapy

According to Huggins and co-workers[21a, 21b] a combination of progestogens and oestrogens gives good remissions.

These authors found the same results in humans with carcinoma of the female breast as in rats with mammary carcinoma induced by dimethyl-benzanthracene. Similarly, ethinyl norethisterone acetate without the addition of oestrogens is a successful form of treatment in 40 per cent of cases[22b, 22c].

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[12] *Luft, R., Olivecrona, H., & Ikkos, D.:* Acta endocr. **31**, 241 (1957).

[13] *Loeser, A. A.:* Brit. Med. J. **4133**, 479 (1940).

[14] Council on Pharmacy and Chemistry: J. Amer. Med. Ass. **146**, 471 (1951).

[15] *Segaloff, A.:* Cancer **5**, 1179 (1952); **8**, 82 (1955); **8**, 785 (1955); **8**, 903 (1955).

[16] *Gellhorn, A., et al.:* J. Amer. Med. Ass. **154**, 1274 (1954).

[17] *Prudente, A.:* Surg. Gyn. Obstetr. **80**, 875 (1945).

[18] *Adler, U.:* Praxis **50**, 956 (1961).

[19] *Friedrich, K.:* Zschr. ärztl. Fortbild. **55**, 324 (1961).

[20] *Stoll, B. A., & Ellis, F.:* Brit. Med. J. **4870**, 796 (1953).

[21] *Lemon, H. M.:* Ann. Int. Med. **46**, 457 (1957).

[21a] *Landau, R. L., et al.:* J. Amer. Med. Ass. **182**, 632 (1962).

[21b] *Huggins, C.:* J. Amer. Med. Ass. **186**, 481 (1963).

[22] *Nissen-Meyer, R.:* Acta endocr. **31**, 314 (1957); Endocrinological Meeting, Edinburgh (1959).

[22b] *Curwen, S.:* Clinic. Radiology **14**, 445 (1963).

[22c] *Curwen, S.:* J. endocrinol. **28**, 3 (1964).

### i) Management

In selected cases, long-term treatment with hormones is indicated. If a remission occurs, it should do so within 4 weeks of starting treatment. If no remission is seen after this lapse of time, the drug being used should be changed or ablative surgery should be considered. What type of treatment and dosage are necessary in selected cases?

1. Measures to avoid recurrence after operation or radiotherapy: In women who are sexually mature, castration should always follow treatment of the primary lesion except in very early cases. Lesions which are stage II or more should be treated with prophylactic testosterone in view of their high recurrence rate.
Dose: Testoviron Depot (Primoteston Depot) 100 to 200 mg. every 2 weeks for 6 months to one year.

2. Treatment of incurable cases in sexually mature women:
Castration and high dosage testosterone therapy:
Testoviron Depot (Primoteston Depot) 250 mg. every 10 to 14 days for as long as possible.

3. Oestrogen therapy in incurable cases occurring in women over 55 years of age.
Dose: 0.4 mg. of ethinyl oestradiol three times a day or 40 mg. Progynon Depot (Primogyn Depot) at weekly intervals.

4. Three tablets of SH 420 (Primolut-Nor 10 mg.) daily.

5. If the above measures fail, treatment with glucocorticoids or hypophysectomy should be tried, regardless of age.
Dose: Prednisolone tablets, 10 mg. daily.

## II. Uterine Carcinoma

### a) Carcinoma of the Cervix

Carcinoma of the cervix does not appear to be hormone dependent. Oestrogens have not been shown to stimulate[23] or inhibit[24] tumour growth. Testosterone, equally, does not make this type of neoplasm regress although some[25, 26] have reported a transient reduction of growth rate.

The beneficial action of this drug is probably due to its influence on metabolism (the anabolic action of sex hormones) and to its psychologically stimulating effect which is also a characteristic of anabolic hormones[30]. The results of androgen therapy in cases of genital tract carcinoma can be summarized[28]:

Favourable psychological effect with occasional euphoria.

Stimulation of appetite and weight increase in cachectic patients.

Improvement of pain.

Increased tolerance to radiotherapy (?).

Inhibition of tumour growth in favourable cases.

In a few cases, these more or less marked effects are seen for a matter of several months, sometimes years. Freedom from pain and a general feeling of well-being almost make a patient forget her advanced disease. The time for which an individual is bedridden, cachectic and suffering from pain which requires morphia is diminished[29]. The end tends to come very suddenly.

**Suggestions for Treatment:**

Testoviron Depot (Primoteston Depot) 250 mg. or Primobolan Depot 200 mg. each every 10 to 14 days.

*Preliminary treatment of cervical carcinoma*

Hormone treatment has been suggested as a preliminary to radium applications in cases of carcinoma of the cervix[31]. Particularly where radiotherapy is successful, oestrogens may assist regeneration and revitalization of damaged tissues. Operative difficulties and complications can often be avoided and figures for permanent cure are improved[32, 33].

**Suggestions for Treatment:**

Progynon Depot (Primogyn Depot) 20 to 30 mg. x 1.

[23] *Wied, G. L.:* Geburtsh. u. Frauenkh. **13**, 492 (1953).
[24] *Wimhöfer, H.:* Strahlenterapie 97, 338 (1955).
[25] *Weghaupt, K.:* Wien. klin. Wschr. **69**, 181 (1957).
[26] *Haas, E., & Verhagen, A.:* Zbl. Gynäk. **76**, 260 (1954).
[27] *Picha, E., & Weghaupt, K.:* Wien. med. Wschr. **104**, 734 (1954).
[28] *Graham, J. B., et al.:* Acta Un. int. Canc. **16**, 1291 (1961).
[29] *Vasterling, H. W.:* Dtsch. med. Wschr. **77**, 1222 (1952).
[30] *Reiffenstuhl, G.:* Med. Klin. **56**, 847 (1961).
[31] *Runge, H., & Wimhöfer, H.:* Dtsch. med. Wschr. **76**, 501 (1951).
[32] *Wimhöfer, H.:* Strahlentherapie **97**, 338 (1955).
[33] *Runge, H.:* Ärztl. Praxis **11**, 1231 (1959).

### b) Carcinoma of the Corpus Uteri

Endometrial carcinoma is not as resistant as is carcinoma of the cervix to treatment with hormones. In some advanced cases, high dosage progestogen therapy may be successful and cause partial secretory transformation in tumour tissue[34]. Kaiser denies this effect and has demonstrated that progestogens have an anti-mitotic effect on endometrial carcinoma[35]. Particularly remarkable successes were achieved in patients with lung metastases. Some of these metastases entirely disappeared[36].

**Suggestions for Treatment[37]:**

Proluton Depot (Primolut Depot) 500 mg. every week for as long as possible or Primolut N 30 mg. daily.

## III. Carcinoma of the Ovary

High doses of sex hormone inhibit gonadotrophin production by the anterior pituitary and thus lead to ovarian atrophy if treatment is carried out for long enough. The degree to which a downhill course in advanced cases of ovarian carcinoma can be prevented by hormones is not yet certain. There are occasional reports[38, 27] of favourable results with good remissions.

Hormone therapy is indicated in all women with progressive ovarian carcinoma. It should, however, not come before surgical and radiotherapeutic measures have been undertaken. A combination of radiotherapy and treatment with androgens is particularly well tolerated[39]. Hormone therapy, once started, should continue as long as possible.

Recently a combination of cytotoxic and anabolic drugs has been recommended[40].

**Suggestions for Treatment:**

Testoviron Depot (Primoteston Depot) 250 mg. every 10 to 14 days.

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[34] *Kistner, R. W.:* Cancer **12**, 1106 (1959).
[35] *Kaiser, R.:* Arch. Gynäk. **193**, 13 (1958).
[36] *Kottmeier, H. L.:* Geburtsh. u. Frauenhk. **22**, 1070 (1962).
[37] *Kelley, R. M., & Baker, W. H.:* N. England J. Med. **264**, 216 (1961).
[38] *Köhler, H.:* Zbl. Gynäk. **74**, 780 (1952).
[39] *Prediger, Fr.:* Dtsch. med. Wschr. **76**, 1078 (1951).
[40] *Buttenberg, D., & Träger, F.:* Med. Welt **1962**, 2093.

# O. Hormone Producing Tumours[1]

Hormone producing tumours can occur in any tissue with endocrine function. Only those tumours secreting sex hormones or gonadotrophins will be discussed in this chapter.

A tumour can only produce steroids if it has the necessary enzyme systems. The biosynthetic process inevitably becomes atypical so that too much in the way of androgens, oestrogens or corticoids may be formed. Excessive sex hormone production always leads to inhibition of gonadotrophin production by the anterior pituitary and thus to suppression of the menstrual cycle. Thus, amenorrhoea is an almost invariable symptom in sexually mature women. Tumours in the anterior pituitary or its neighbourhood may also influence ovarian function. The inhibition of gonadotrophin excretion may ultimately be mechanical and due to compression of the cells secreting gonadotrophins by tumour tissue[2].

## I. Tumours of the Ovary

Ovarian tumours may both masculinize and feminize[3] and histological examination shows no relationship with any associated hormone effect. Rarely, cases of chorion-epithelioma of ovarian origin may be seen.

The oestrogen producing tumours, sometimes called "oestroblastomas" include the granulosa cell tumours[4], the theca cell tumours and the luteomas[5]. It can also be assumed that ovarian tumours such as pseudomucinous cystadenomas and other cystadenomas also produce small quantities of oestrogens. This has been shown by the examination of vaginal smears in these cases[6].

The granulosa cell tumours which commonly arise at about the time of the menopause are usually unilateral and may achieve considerable dimensions. They are malignant, showing a tendency to recur.

Areas of softening, fibrosis and cyst formation may be seen macroscopically. The yellowish colour and corresponding histochemical

[1] *Hennig, H. D.:* Internist 4, 24 (1963).
[2] *Oberdisse, K.:* IV. Symposium für Endokrinologie 45, Berlin (1956).
[3] *Lins, H.:* Ärztl. Wschr. 12, 963 (1957).
[4] *Kleine, H. O.:* Arch. Gynäk. 155, 168 (1933).
[5] *Dubrauszky, V.:* Arch. Gynék. 176, 726 (1949).
[6] *Wren, B. G., & Frampton, J.:* Brit. Med. J. 5361, 842 (1963).

characteristics suggest that the tumour has a significant lipoid content. Microscopically, some areas show apparent granulosa cells.

Theca cell tumours remain relatively small and are almost always seen in older women. These tumours, which are often not palpable, should be suspected in post-menopausal women with vaginal bleeding and proliferative endometrium. The signs and symptoms resemble those seen with prolonged oestrogen therapy. Generally speaking, theca cell tumours are solid in consistency and yellowish in colour. The benign tumours resemble fibromas or ovarian sarcoma histologically and theca cell elements are also found. It is not generally accepted that luteomas (which produce oestrogens, progesterone and androgens and contain theca and granulosa cells) should be grouped separately[7].

Animal experiments aimed at observing the response of the ovary to high-level gonadotrophin stimulation throw an interesting light on hormone producing tumours. Para-biotic experiments[9] using two or three animals with only one ovary between them as well as intrasplenic ovarian transplants have been used[10]. Under these circumstances, granulosa cell tumours could be produced and there can be little doubt about their aetiology. The results do not, however, allow one to conclude whether these neoplasms are truly autonomic and malignant or whether they represent compensatory hypertrophy as suggested by *Büngeler*[11].

Masculinizing tumours of the ovary are very rare. In addition to the polycystic ovaries of *Stein-Leventhal* syndrome (page 83), two types of tumour may be distinguished[12]. Arrhenoblastomas contain mesenchymal and epithelial elements found in the normal ovary. These tumours have been observed at all ages and may be malignant. The enzymatic processes leading to increased androgen production have been studied[13]. These tissues are not able to synthesize oestrogens from androgens (page 10). In additon, tumours have been described whose histological appearance resembles adrenal tissue. These are thought to be neoplasms arising in ectopic adrenal remnants. The main feature of patients with androgen producing tumours are general virilization and a moderate increase in 17-ketosteroid excretion. Measurement of the fractionated separate hormones in this group are of diagnostic importance. With ovarian tumours, there is a selective increase in the excretion of compounds with α-linkages (testosterone, androsterone, aetiocholanone)[15]. An increased excretion of β-ketosteroids (dehydro-androsterone) suggests adrenal neoplasm. The use of dexamethasone and chorionic gonadotrophin is also important for differential diagnosis (page 84): a fall in excretion during dexamethasone treatment suggests adrenal hypertrophy[16] (page 85). If the excretion of 17-ketosteroids remains unchanged, this suggests an ovarian tumour (figure 82). A rise in the excretion of 17-ketosteroids has been observed during chorionic gonadotrophin therapy in cases with androgen producing ovarian tumours[17].

Malignant chorion-epithelomata of ovarian origin have been observed in adults and children. They should be viewed in the same light as testicular tumours which are also thought to represent neoplasms arising in foetal cell remnants[18, 19]. For this reason they are also known as ectopic chorion-epitheliomata.

Their pathogenesis is quite distinct from cases of chorion-epithelioma which only arise after normal pregnancy or hydatidiform moles. The main criterion for diagnosing chorion-epithelioma is the raised excretion of chorionic gonadotrophin. Levels of 100,000 IU a day may be attained (page 115).

## II. Adrenal Cortical Tumours

The histological appearance of adrenal cortical tumours does not provide any clues

[7] *Novak, E.:* Amer. J. Obstetr. Gynec. **63**, 294 (1952).
[8] *Nevinny-Stickel, J.:* Deutsch. med. J. **13**, 750 (1962).
[9] *Mühlbock, O.:* Geburtsh. u. Frauenhk. **12**, 289. (1952).
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[14] *Landing, B. H., & Gold, E.:* J. Clin. Endocr. **11**, 1436 (1951).
[15] *Winzler, H., et al.:* Schweiz. med. Wschr. **87**, 1562 (1957).
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[17] *Gilbert-Dreyfus, Z., et al.:* Sem hôp. **32**, 3921 (1956).
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[19] *Gropler, D., & Sauerteig, E.:* Geburtsh. u. Frauenhk. **16**, 58 (1956).

about hormone function. In theory, adrenal tumours can produce glucocorticoids (*Cushing's* syndrome), mineralocorticoids and sex hormones.

*Androgen producing tumours.* Adrenal neoplasms, in spite of a histological resemblance both to tumours causing *Cushing's* syndrome and tumours causing feminization, may secrete androgens[20, 21]. They are usually carcinomatous and sometimes adenomatous. These tumours may be so small that they are missed by palpation or radiographic examination

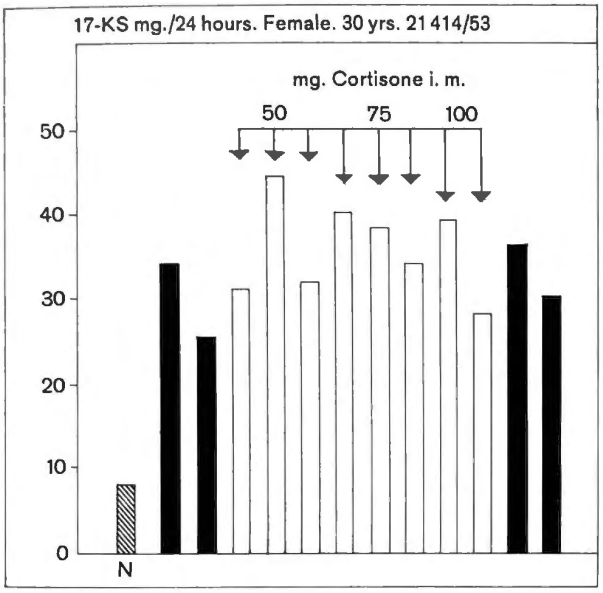


Figure 82. Cortisone test in a patient with an adrenal tumour. There is no fall in 17-ketosteroid excretion. (*Würterle, A.:* Deutsch. Gesd.wes. 11, 1705 [1956])

(intravenous pyelography with presacral air insufflation). Their cut surface is yellowish and histologically they resemble adrenal tissue although macroscopic appearances suggest no such relationship. Adrenal tumours should be suspected in all cases, particularly children, showing evidence of virilism in whom an ovarian tumour has been excluded. Congenital forms of this disorder are usually due to adrenal dysfunction (adreno-genital syndrome) and are commonly associated with some degree of malformation (page 84). *Cushing's* syndrome may be seen in cases showing virilization due to adrenal tumour. It is important to distinguish between adrenal tumours and adrenal dysfunction as the treatment is different in each case. The behaviour of 17-ketosteroids (= 17-KS) is of critical importance in this respect (figure 82):

The 24-hour excretion of urinary 17-ketosteroids, particularly dehydro-epi-androsterone, may be raised.

These values do not fall during treatment with cortisone as in cases of adrenal hyperplasia. An increase of 17-ketosteroid excretion following injections of chorionic gonadotrophin is characteristic of ovarian tumours and need not be expected here. The presence of a tumour is also suggested by a negative family history and the absence of malformations.

Adrenal tumours can only be treated by surgery while cortisone therapy may be indicated in cases of adreno-genital syndrome (page 84).

Oestrogen secreting adrenal tumours are very rare. A few cases of carcinoma have been observed in men. They are associated with gonadal atrophy and gynaecomastia[22].

In conclusion, it should be mentioned that hormone producing adenomas can be produced experimentally in some animals by early castration[23]. These findings cannot be applied to human beings.

## III. Tumours of the Anterior Pituitary

Anterior pituitary tumours with raised gonadotrophin excretion values are relatively rare when compared to those tumours which produce ACTH (basophil adenomata) and those which produce growth hormone (eosinophil adenomata). A few cases of chromophobe adenoma have been described in which amenorrhoea and excessive lactation have occurred[24]. It is probable that these tumours secrete prolactin (page 43).

[20] *Gebauer, A., & Linke, A.:* Dtsch. med. Wschr. 14, 456 (1951).

[21] *Held, E.:* Acta endocr. 17, 128 (1954).

[22] *Wilkins, L.:* J. Clin. Endocr. 8, 111 (1948).

[23] *Houssay, B. H., et al.:* Schweiz. med. Wschr. 85, 291 (1955).

[24] *Forbes, A. P., et al.:* J. Clin. Endocr. 14, 265 (1954).

# P. Hormone Therapy with Gynaecological Operations

## I. Treatment of Post-operative Shock

An operation represents what *Selye* describes as stress and affects the circulation as well as the metabolism of proteins and electrolytes[1]. The body produces a typical alarm reaction. The adrenal responds by an increased secretion of corticosteroids. If the body adapts itself inadequately or there is transient adrenal insufficiency, a state of shock results which can be somewhat difficult to treat with blood transfusion, circulatory stimulants etc.

This condition may be recognized by the absence of anaemia. the appearance of loin tenderness not immediately after the operation but some hours later, extreme thirst, hypotension and albuminuria[2]. In addition, there is no usual rise in 17-ketosteroid excretion.

**Treatment:**

Rapid administration of hydrocortisone, preferably by the intravenous route, in order to counter the basic cause of the patient's collapse.

Dose: 100 mg. of an intravenous hydrocortisone preparation by intravenous infusion over a period of 2 to 6 hours.

## II. Hormone Therapy before Major Operations

The risk of major operations can be diminished by preparing patients mentally and physically[3]. To this end, a single large dose of testosterone has a stimulant effect. The patient's initial condition is improved in the following way[4]: Testosterone has an anti-depressive effect and makes the patient euphoric. Testosterone has an anabolic action. Protein loss resulting from operation is minimized[3].

Testosterone protects adrenal function[5]. Exhaustion of this endocrine gland is prevented.

**Treatment:**

Testoviron Depot (Primoteston Depot) 100 mg. the day before operation together with cortisone depot 250 mg.

---

[1] *Rehn, J.:* Langenbecks Arch. klin. Chir. **278**, 229 (1954); **272**, 21 (1952).

[2] *Taylor, E. S., & Essig, L. L.:* Amer. J. Obstetr. Gynec. **65**, 720 (1953).

[3] *Hegemann, G.:* Geburtsh. u. Frauenhk. **14**, 97 (1954).

[4] *Flückiger, P.:* Schweiz. med. Wschr. **81**, 1174 (1951).

[5] *Zizine, L. A., Simpson, M. E., et al.:* Endocrinology **47**, 97 (1950).

## III. Operations during Pregnancy

Every operation is a stress situation and may lead to transient disturbances in circulation and metabolism. In pregnant women, there is a risk of miscarriage which may well be due to post-operative complications rather than to anaesthesia and the direct effect of surgical intervention.

If operative procedures involve the pregnant uterus (e.g. myomectomy) or the adnexal structures, there is an increased risk of abortion as uterine contractions can hardly be avoided with this type of surgery. The chance of preserving the pregnancy may be increased by damping down uterine activity with progestogens[6].

Cervical insufficiency is an important indication for operation. By using the *Shirodkar* technique the cervix can be closed until the end of pregnancy. Protective hormone therapy using progestogens is recommended with these operations[7].

It is interesting to speculate whether removal of the corpus luteum in the early weeks of pregnancy has any effect. There is no doubt that the placenta starts producing sex hormones at a very early stage (page 32) and that removal of the corpus luteum after the third month does not set the pregnancy at risk[8, 9]. In spite of this, it would seem advisable to treat all patients where the corpus luteum of pregnancy has been removed with high doses of progestogen preferably starting at the time of operation.

**Treatment:**

Proluton Depot (Primolut Depot) 500 mg. 1 to 2 days before operations on the pregnant uterus.

The injection should be repeated 4 days later.

## IV. Oestrogen Therapy with Plastic Vaginal Surgery

The state of the vaginal epithelium depends largely on the presence or absence of oestrogens (page 58). There is experimental evidence to show that vaginal wounds heal more slowly in the absence of ovarian function[10].

The use of oestrogen creams after operations to create an artificial vagina is of great practical importance[11]. The cream acts as a lubricant, promotes epithelial regeneration and prevents scarring and shrinkage of the artificial vagina. Vaginal epithelium usually heals well after operations for prolapse so that oestrogen therapy need not follow this type of surgery.

[6] *Gitsch, E.:* Wien. klin. Wschr. **69**, 348 (1957).
[7] *Hefner, J. D., et al.:* Obstet. & Gynec. **18**, 616 (1961).
[8] *Herrmann, U.*, u. *Matter, R.:* Geburtsh. u. Frauenhk. **16**, 690 (1956).
[9] *Simon, J.:* Bull. Soc. belge gynéc. obstétr. **25**, 126 (1955).
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[11] *Ripman, H.:* Lancet **6711**, 744 (1952).

# Chapter Q:

# Table of the Most Frequently used Hormone Preparations

**I. Oestrogens**

| Composition | Preparation | Form of application | Proliferation dose in mg. | Estimated duration of action following a single application in days |
|---|---|---|---|---|
| Oestradiol valerate | Progynon Depot | i.m. | 20—30 | 12—14 |
| Ethinyl oestradiol | Progynon C | oral | 2 | — |

**II. Progestogens**

| Composition | Preparation | Form of application | Transformation dose in mg. | Duration of action in days |
|---|---|---|---|---|
| 17α-hydroxy-progesterone caproate | Proluton Depot | i.m. | 250 | 8—10 |
| Norethisterone | Primolut N | oral | 100—150 | — |
| Norethisterone acetate | Primolut-Nor 10 mg. | oral | 30—60 | — |

**III. Androgens**

| Composition | Preparation | Form of application | Estimated duration of action in days | |
|---|---|---|---|---|
| Testosterone oenanthate with and without testosterone propionate | Testoviron Depot | i.m. | 14—20 | |

**IV. Anabolic Agents**

| Composition | Preparation | Form of application | Estimated duration of action in days | |
|---|---|---|---|---|
| 1-methyl-$\Delta^1$-androstenolone oenanthate | Primobolan Depot | i.m. | 14 | |
| 1-methyl-$\Delta^1$-androstenolone acetate | Primobolan | oral | — | |

**V. Progestogen/Oestrogen Combinations**

| Composition | Preparation | Form of application | Duration of action in days | Indications |
|---|---|---|---|---|
| Progesterone and oestradiol benzoate | Duogynon (in Belgium: Proluton Z Fort) | i.m. | 4 | Secondary amenorrhoea<br>Postponement of menstruation<br>Pregnancy diagnosis |
| Oestradiol benzoate and 17α-hydroxy-progesterone caproate | Primosiston | i.m. | 10 | Postponement of menstruation |
| Norethisterone acetate and ethinyl oestradiol | Duogynon | oral | | Secondary amenorrhoea<br>Pregnancy diagnosis |

**VI. Contraceptives**

| Composition in mg. | Preparation | Form of application | | |
|---|---|---|---|---|
| 4 mg. norethisterone acetate and 0.05 mg. ethinyl oestradiol | Anovlar 21 | oral | | |
| 3 mg. norethisterone acetate and 0.05 mg. ethinyl oestradiol | Gynovlar 21 | oral | | |

**VII. Oestrogen/Androgen Combinations**

| Composition | Preparation | Form of application | Duration of action in days | Indications |
|---|---|---|---|---|
| Oestradiol valerate and testosterone oenanthate | Primodian Depot | i.m. | 21 | Climacteric disorders Osteoporosis |
| Ethinyl oestradiol and methyltestosterone | Primodian | oral | | Deafness in the ageing Circulatory disturbances |

**VIII. Chorionic Gonadotrophin**

| Strength | Preparation | Form of application | | |
|---|---|---|---|---|
| 1000 I.U.<br>5000 I.U. | Primogonyl | i.m. | | |

**IX. Serum Gonadotrophin**

| Strength | Preparation | Form of application | | |
|---|---|---|---|---|
| 1000 I.U. | Anteron | i.m. | | |

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